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SHORT COMMUNICATION

The Missing Link in the Diagnostic Pathway of Prostate Cancer

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Abstract Prostate cancer is one of the most common cancers in the Western world. It is among the leading causes of cancer related death. While its incidence and survival increased significantly during the last few decades in Denmark, the mortality rate did not change for patients younger than 80 year old. Development of new techniques, such as multiparametric MRI, helps to increase the accuracy of diagnosis. However, a missing link in the diagnostic pathway may result in mistreatment if an acinar adenocarcinoma of prostate is transformed into a neuroendocrine phenotype such as small cell carcinoma.

Keywords Prostatic carcinoma · Adenocarcinoma · Small cell carcinoma · Immunohistochemistry

Introduction

Small cell carcinoma is an aggressive tumour of the prostate, usually with a short period of survival. The diagnosis of prostatic small cell carcinoma (PSCC) is important because this tumour is resistant to most therapies of prostate cancer, such as hormonal therapy, castration and conventional therapy of castration resistant prostate cancer. If accurate early diagnosis of PSCC is not made, the patient may be attempted to be treated according to a prostate adenocarcinoma regime, which can be ineffective. This is even more important if the tumour is mixed, and an early biopsy is consistent with acinar adenocarcinoma only. Therefore, in such cases, the lethal component of PSCC may not be treated.

Results

The presence of undiagnosed and therefore untreated PSCC in a patient suffering from prostate cancer is important due to the aggressive nature of the disease. The occurrence of PSCC is difficult to document because many of these cases do not undergo autopsy, or histology is not performed during autopsy. Obviously, its precise incidence needs to be determined. We would like to describe a typical example, which shows this missing link in the diagnostic pathway of prostate cancer.

Case Presentation

A 68 year old male patient presented with lower urinary tract symptoms (LUTS) and elevated PSA of 32,1 μg/l in September 2012. He had a history of severe cerebral stroke in 2007 but no other known disease. Due to his poor performance status as a result of stroke, transrectal ultrasound (TRUS) examination and diagnostic prostate biopsies were not attempted. However PSA, measured in November 2014, increased to 53 μg/l. se-Creatinin was also increased. The patient was treated with dialysis due to renal insufficiency. The pathophysiology of the renal insufficiency was not well understood, and there was only mild hydronephrosis. CT of thorax and abdomen at that time showed no metastases and a normal sized prostate.

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After worsening of his renal condition, diagnostic needle core biopsies of the prostate were performed in December 2014, which showed acinar adenocarcinoma in 5 of 6 biopsies with a composite Gleason score 3 + 4. Bone-scintigraphy was negative. After discussing the patient at a multidisciplinary team (MDT) meeting, it was decided that he was not candidate for curative treatment. Therefore in agreement with the Danish national guidelines, he was given non-curative treatment of gonadotropin releasing hormone agonist Eligard (Leuprorelin, 45 mg) together with anti-androgen Bicalutamid (50 mg).

Twenty days after the bone-scintigraphy, MRI was performed in an attempt to identify the cause of hydronephrosis. It showed multiple tumour metastases in the liver and bones, and the extension of a tumour to the urinary bladder. Severe thrombocytopenia (13×10^9/l) had developed, which raised the suspicion of bone marrow insufficiency. The patient developed multiorgan failure, his clinical status deteriorated rapidly, and he died 53 days after the prostate biopsies. His PSA fell to 13.2 μg/l just prior to the time of his death. PSCC had never been diagnosed in his life-time.

Post Mortem Examination

Autopsy was performed and tissue blocks for histological examination were selected from prostate, bladder, rectum, liver, lungs, spleen, pancreas, small and large intestines, kidneys, heart and bone marrow. 3 μm thick sections of the diagnostic prostate needle core biopsies and autopsy material were cut from paraffin blocks and stained with haematoxylin and eosin (HE) in Leica ST4040.

Immunohistochemistry, including heat mediated antigen retrieval, was performed in Ventana Benchmark Ultra with the Ventana OptiView DAB IHC Detection Kit. The panel of antibodies for proteins such as cytokeratins (PCK) (DAKO, AE1/AE3, 1:50), prostate specific antigen (PSA) (DAKO, polyclonal rabbit, 1:10,000), CD56 (Cell Marque, MRQ-42, 1:400), synaptophysin (Thermo Scientific, SP11, 1:50), chromogranin (DAKO, polyclonal rabbit, 1:2000), thyroid transcription factor-1 (TTF-1) (Novocastra, SPT 24, 1:50), cytokeratin 7 (DAKO, OV-TL 12/30, 1:800), cytokeratin 20 (DAKO, Ks20.8, 1:50), P53 (DAKO, DO-7, 1:100) was selected in attempt to identify tumour type and differentiation.

The autopsy revealed a pelvic tumour involving the prostate, bladder and rectum. There were multiple tumour deposits consistent with metastases in the liver and spine. There was no tumour in the lungs. Microscopic examination of the tumour involving the prostate showed only small areas of acinar adenocarcinoma with the rest of the tumour being PSCC. Immunohistochemistry of acinar adenocarcinoma was positive for PSA and PCK, but it was negative for TTF-1. There was variable, focal staining for the neuroendocrine (NE) markers of synaptophysin, chromogranin and CD56, from none to sometimes quite strong, consistent with NE differentiation, which seemed to coincide with focal P53 expression in this area. In contrast, PSCC was diffusely and strongly positive for P53. It was also positive for TTF-1, PCK, synaptophysin, chromogranin and CD56, but negative for PSA (Fig. 1). There were areas of transition between acinar adenocarcinoma and PSCC (Fig. 2), where the malignant cells lost expression of PSA and gained expression of P53, and to some extent, the NE markers.

Following autopsy, the HE sections of the original diagnostic needle core biopsies taken in December 2014 were reviewed and no morphological or immunohistochemical evidence of PSCC was found.

The Missing Link in the Diagnostic Pathway (Review of Guidelines)

As in the present case, clinicians may notice the occurrence of metastasis in a patient previously diagnosed with prostatic acinar adenocarcinoma, and they may decide to treat it as metastatic prostatic acinar adenocarcinoma. If treatment appears ineffective, biopsy may be taken. However, the diagnosis of PSCC in a needle core biopsy from a distant metastasis, if taken, is challenging because PSCCs are usually negative for prostate specific markers such as PSA. Therefore, careful clinico-pathological and radiological correlation is required in order to determine the site of origin as prostatic in a case of metastatic small cell carcinoma, usually by exclusion of other primary sites such as lung. This prompts the suggestion that an early biopsy would be required from a metastasis thought to be arising from a prostate cancer, which is unresponsive to conventional therapy. However, in the current clinical practice it is not performed routinely. Neither the American Urological Association (AUA) nor the European Association of Urology

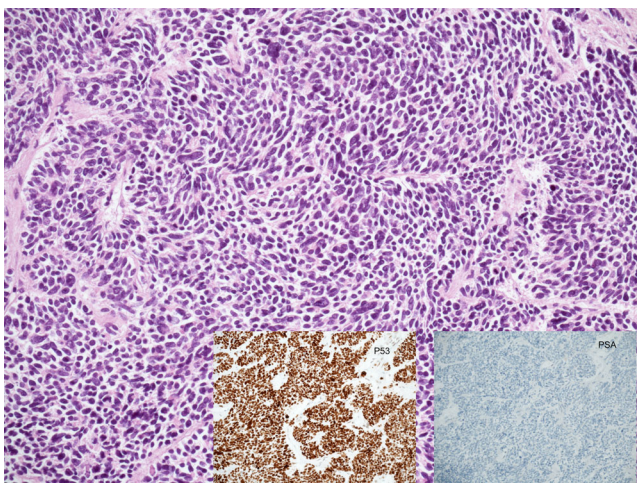

Fig. 1 Prostatic small cell carcinoma (metastasis in liver). Inset: immunohistochemistry for PSA and p53

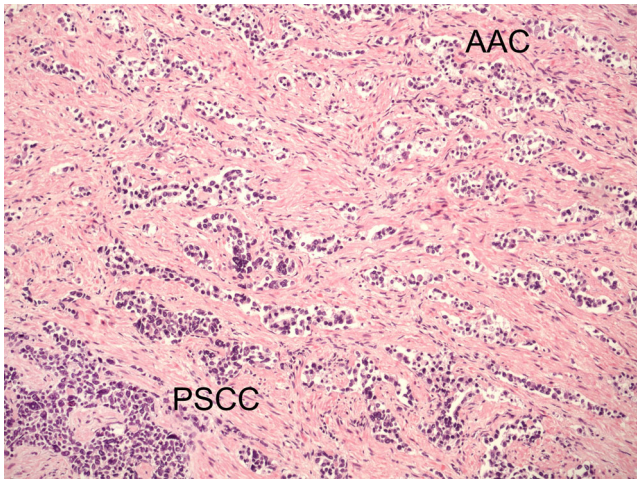

Fig. 2 AAC: Acinar adenocarcinoma of prostate, PSCC: Prostatic small cell carcinoma

(EAU) guidelines suggests a biopsi from a suspected PC metastasis, if other type of tumor in another organ is not suspected [1, 2].

Discussion

Prostate cancers may develop from different cell types in the prostate such as acinar, ductal, basaloid or NE cells. Small cell carcinoma of the prostate is rare and estimated to account for less than 2% of all prostatic malignancies [3]. It is a highly aggressive form of tumour with a median survival of 7–13.1 months, but most studies have reported less than one year [3, 4]. It is negative for androgen receptor, does not respond to hormonal therapy and is castration resistant [5]. The tumour is thought to be poorly differentiated NE tumour and therefore the cells of PSCC are usually positive for NE markers such as chromogranin, synaptophysin, neuron-specific enolase and CD56, but negative for PSA [6].

Neuroendocrine cells are known to be present in normal prostate with a function of providing trophic signals to normal epithelial cells [6]. However, all prostate adenocarcinomas show focal sparse NE cells, and 5–10% of them show zones with more extensive population of NE cells. The prognostic significance of this is controversial. It has been described that NE cells can stimulate the growth of surrounding adenocarcinoma cells [6], and that adenocarcinoma cells can transdifferentiate into NE cells [7].

In theory, PSCC can arise either de novo, or from pre-existing NE cells of prostate, or from prostatic epithelial cells via transdifferentiation [6, 7]. Commonly, PSCC occurs in patients with high-grade adenocarcinoma treated with androgen deprivation therapy, but they usually have no benefit from this treatment. Due to the possibility of epithelial cell transdifferentiation into NE cells, such as PSCC cells, it has been suggested that hormonal therapy may drive the cells of an acinar adenocarcinoma into NE cells [7]. With the availability of more efficient drugs on the market one might fear an increase in the incidence of PSCC.

The clinical behaviour of PSCC is usually characterized by extensive local disease, visceral disease, lytic bone lesions and low PSA levels despite large metastatic burden [3]. Elevated serum-LDH and low serum-albumin at the time of diagnosis is believed to worsen the prognosis [4].

Treatment options for PSCC are limited. Patients with PSCC are usually treated with platinum based chemotherapy rather than androgen receptor targeted hormonal therapies [8], which usually produces a good response of short duration [9]. However, better and more successful management of this aggressive and lethal disease is required. Promising results have been shown with targeting the p53 pathway. PSCC is usually negative for PSA and positive for p53 suggesting the mutation of the p53 gene [5]. Li et al. proposed a possible mechanism for p53 mutation leading to the development of PSCC via the inactivation of the IL8-CXCR2-p53 pathway [5]. It has also been shown that p53 mutation leads to Aurora kinase A expression, which is critically important for the rapid proliferation and aggressive behaviour of PSCC [5]. In addition, a 50 gene expression signature of NE prostate cancer has been presented, recently [10]. Therefore, developing special therapies targeting individual potentially pathological genes or signalling factors, such as development of effective Aurora kinase A inhibitors might lead to better and more successful management of this aggressive and lethal disease.

However, PSCC may not be clinically diagnosed in a patient whose initial diagnostic needle core biopsies show the acinar component of a prostate carcinoma. Therefore, we suggest that clinical and biochemical markers should be identified, which may suggest the appearance of PSCC. The suspicion should arise, if such patient undergoes a sudden and progressive clinical relapse, which can not be observed in PSA levels. If metastasis develops in such a prostate cancer patient, a biopsy from it should be taken for histological examination as early as possible in order to obtain an accurate diagnosis of PSCC, which is required for proper treatment and adequate management of the patient.

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