Pathology & Oncology Research (2020) 26:1447–1450
https://doi.org/10.1007/s12253-019-00712-2

ORIGINAL ARTICLE

Neuroendocrine Cancer of the Prostate

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Received: 21 May 2019 / Accepted: 6 August 2019 / Published online: 14 August 2019

Abstract

Neuroendocrine cancer of the prostate is considered to be a rare entity with bad prognosis and limited therapeutic options. We performed a prospective analysis of the patients treated in our hospital for prostate cancer between 1st January 2015 and 31rd December 2018. Neuroendocrine phenomena were tested by immunohistochemistry and laboratory chemistry on the request of the clinicians in the cases when a positive diagnosis was suspected. Clinical tableaux of high suspicion of neuroendocrine cancer included radiological progression of a metastatic disease without PSA rise, relatively extended metastatic disease associated to a low PSA, disease with non-pulmonary visceral metastases. 10 patients were diagnosed with neuroendocrine tumour out of 521 prostate cancers. Half of the patients had a survival over a year. 3 patients received 3 lines of efficacious palliative chemotherapy. 1 patient underwent prostatectomy after neoadjuvant chemotherapy for a localised disease. The incidence of neuroendocrine tumours among prostate cancer patients was higher than expected. Some of the patients had a relatively good outcome.

Keywords Neuroendocrine · Prostate cancer · Immunohistochemistry · Serum marker · Platinum

Introduction

Neuroendocrine cells are present in the prostatic tissue [1], but their identification by hematoxylin-eosin (HE) stain is impossible due to their rarity [2]. Neuroendocrine cancer of the prostate may develop in single or multiple foci within an adenocarcinoma and also de novo as an individual tumour. In the second case it may present as small cell or more rarely as large cell carcinoma. Carcinoid tumours can also be localised in the prostate [2, 3], Table 1.

The incidence of neuroendocrine prostate cancer is considered to be extremely low. In the SEER database between 2004 and 2013 0.06% of the over 500.000 prostate cancers were de novo neuroendocrine cancers [4]. In our hospital only 1 case of neuroendocrine prostate cancer was registered between 1995 and 2015 (unpublished data).

The therapeutic resources are also considered to be scarce being limited to the platinum-etoposide palliative chemotherapy [5].

Patients and Methods

We performed a prospective analysis of the patients treated in our hospital for prostate cancer between 1st January 2015 and 31rd December 2018. Neuroendocrine phenomena were tested by immunohistochemistry and laboratory chemistry when clinicians suspected the diagnosis. The neuroendocrine staining was realised in all but some rare cases on the explicit asking of the clinicians.

The diagnosis of neuroendocrine cancer was retained in case the neuroendocrine markers showed positive staining by immunohistochemistry or the elevation of a neuroendocrine serum marker (NSE or chromogranine A) was associated to a disseminated disease with low PSA level. In the second case a favourable radiological response to a platinum-etoposide combination

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Table 1 Subtypes of neuroendocrine tumours of the prostate

Neuroendocrin differentiation of an adenocarcinoma
single focus
multiple foci
De novo neuroendocrine carcinoma
small cell
large cell
Carcinoid tumour of the prostate

chemotherapy was required for the confirmation of the diagnosis. (Proton pump inhibitors were stopped before dosing chromogranine.)

Results

A total of 521 men were diagnosed with prostate cancer. 10 patients out of 521 showed neuroendocrine phenomena. The mean age at the diagnosis of the neuroendocrine disease was 68.3 years (range: 59–79). The mean time from the diagnosis of prostate cancer to the diagnosis of neuroendocrine differentiation was 36.3 months (range: 0–126). Two patients were diagnosed with de novo neuroendocrine prostate cancer. 9 patients were metastatic, 1 patient's disease was localised to the prostate. The metastatic sites and other patients' characteristics are summarised in Table 2.

7 patients' diagnosis was confirmed by immunohistochemistry (4 on prostate, 2 on lymph node and 1 on liver specimens, see Figs. 1, 2 and 3) and 7 had an elevated level of NSE. Chromogranine A was dosed for only 2 persons who had either normal or slightly elevated NSE and both results showed to be elevated.

5 patients had a survival of less than half a year. 2 of them died of disease progression within a month after diagnosis without or with the administration of salvage chemotherapy. 1 patient died of a heart attack after the first cycle of chemotherapy. 1 patient did not accept any chemotherapy and was lost in four months. 1 patient only received the standard first line chemotherapy and died of disease progression shortly afterwards.

5 patients had a survival over a year. 3 patients received 3 lines of palliative chemotherapy. 1 patient underwent prostatectomy after neoadjuvant chemotherapy for a localised disease. (He was lost of an intercurrent illness without having signs of disease progression.) 1 patient had a very slowly progressive disease and did not accept a second line of chemotherapy. One of the long survivors has a de novo neuroendocrine cancer.

Discussion

Neuroendocrine cancer of the prostate may be suspected in several clinical situations: 1) in a prostate cancer patient followed for metastatic disease and presenting

Table 2 Patient's characteristics and outcome

Patient		Diagnosis					Treatment				Outcome	
	age	IHC	NSE	CgA	PSA	Metastatic sites	1	2	3	4	TTND	OS
1.	76	np	26	121	1.3	bone	6 DDP-VP	RT			126	37
2.	60	pos.	46	np	0.1	bone, liver, urethra	5 DDP-VP				66	6
3.	79	pos.	96	np	70	bone, node, liver, spleen	degarelix				0	4
4.	62	np	>200	np	0.6	bone, liver	1 FEP				42	0
5.	71	pos.	29	np	3.2	bone, node, liver, lung	3 DDP-VP	RT	7 TXT	6 CP-VP	30	>26
6.	64	np	np	np	13.7	bone, node, liver					18	0
7.	68	pos.	9,4	np	16	bone, node, lung	6 DDP-VP	7 TXT	6 TXT-CP		0	>24
8.	59	pos.	71	np	0.1	bone, node, liver	6 TXT	6 DDP-VP	6 TXT-CP	RT	21	18
9.	76	pos.	24	np	0.9		7 DDP-VP	RP			29	14
10.	68	pos.	13	333	12.4	bone, liver	1 DDP-VP				41	1

IHC immunohistochemistry, *NSE* neuron specific enolase, *CgA* chromogranin A, *PSA* prostate specific antigen, *TTND* time to neuroendocrine differentiation, *OS* overall survival (both in months), *np* not performed, *node* lymph node, *DDP* cisplatin, *CP* carboplatin, *VP* etoposide, *TXT* docetaxel, *FEP* 5-fluorouracil-epirubicin-cisplatin combination therapy, *RT* palliative radiotherapy of bone or lymphoglandular metastases, *RP* radical prostatectomy

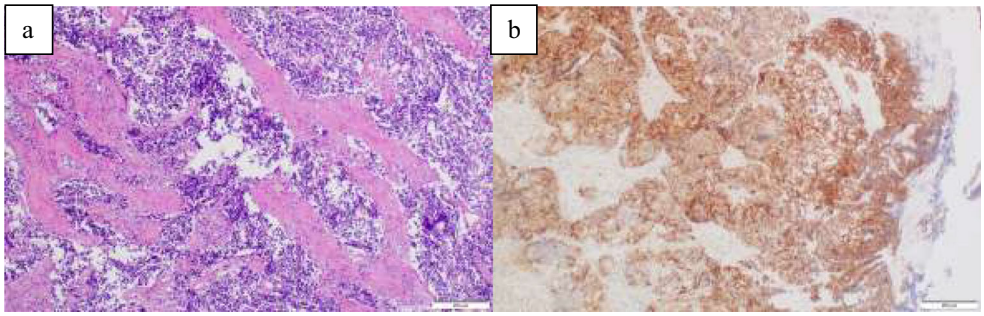

Fig. 1 Patient N°3, transurethral resection of the prostate, HE (**a**) and chromogranine (**b**) staining. De novo neuroendocrine tumour with 90% of small cell and 10% of large cell components

clinical and/or radiological signs of progression despite of a suppressed PSA level, 2) upon the discovery of a relatively extended metastatic disease associated to a low PSA, 3) in any prostate cancer patient with non-pulmonary visceral metastases, 4) facing an adenocarcinoma of unknown primary, that is a multimetastatic disease with usually bone, lymphonodular and even visceral localisations without any evident primary tumour on whole body CT scan. The pitfall of many of these situations is that clinicians tend to eliminate prostate as the origin of the metastatic progression on the basis of a normal or low PSA. Repeating the biopsy of the prostate in case the cancer diagnosis has been established or making neuroendocrine staining for an adenocarcinoma of unknown primary is not part of the clinical routine. Bypassing the pathological diagnosis by laboratory markers such as the non-specific NSE and the rather difficult to access chromogranine A is not convenient either.

Epidemiological data have to be interpreted with caution since the diagnosis of neuroendocrine prostate cancer can be missed. Our case series shows that more cases may be identified by a vigilant attitude.

The pathogenesis of neuroendocrine prostate cancer is not clear. There is evidence that neuroendocrine differentiation may develop as a mechanism of resistance in adenocarcinomas treated by androgen deprivation therapy [2, 3]. In these cases the presence of neuroendocrine foci correlates with higher grade of malignancy [6]. The simultaneous prevalence of malignant cell clones of different characteristics may explain the fact that radiologic regression and long term disease control can be achieved by alternating administration of docetaxel and platinum (Fig. 2). In other cases neuroendocrine phenomena are

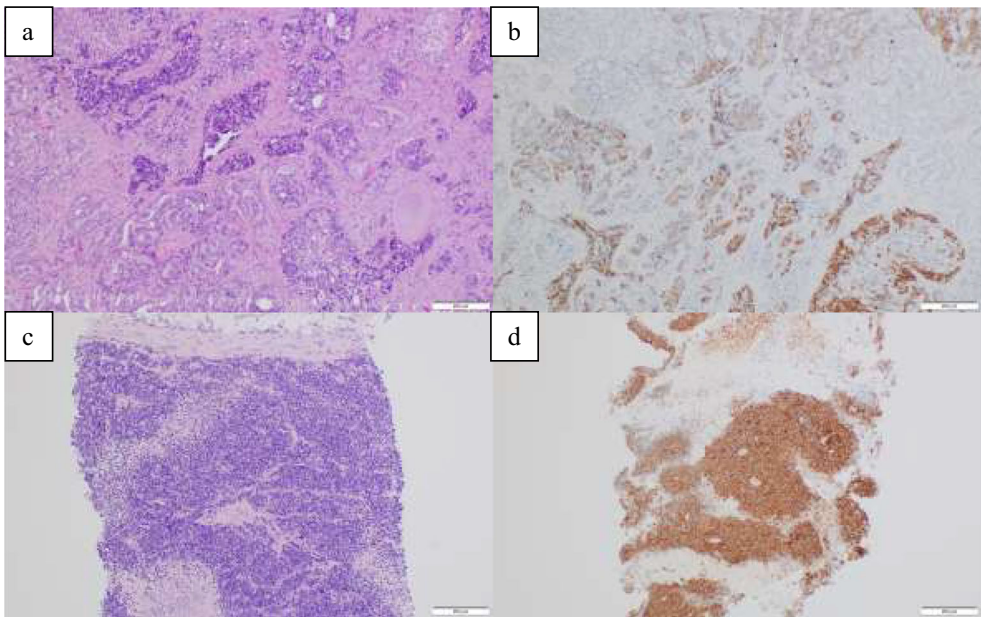

Fig. 2 Patient N°8, prostatectomy, HE (**a**) and retrospective chromogranine (**b**) staining, supraclavicular lymph node metastasis, HE (**c**) and chromogranine (**d**) staining. The mosaic phenomenon of adenocarcinoma and neuroendocrine carcinoma as well as the proportional progression of the neuroendocrine component are represented

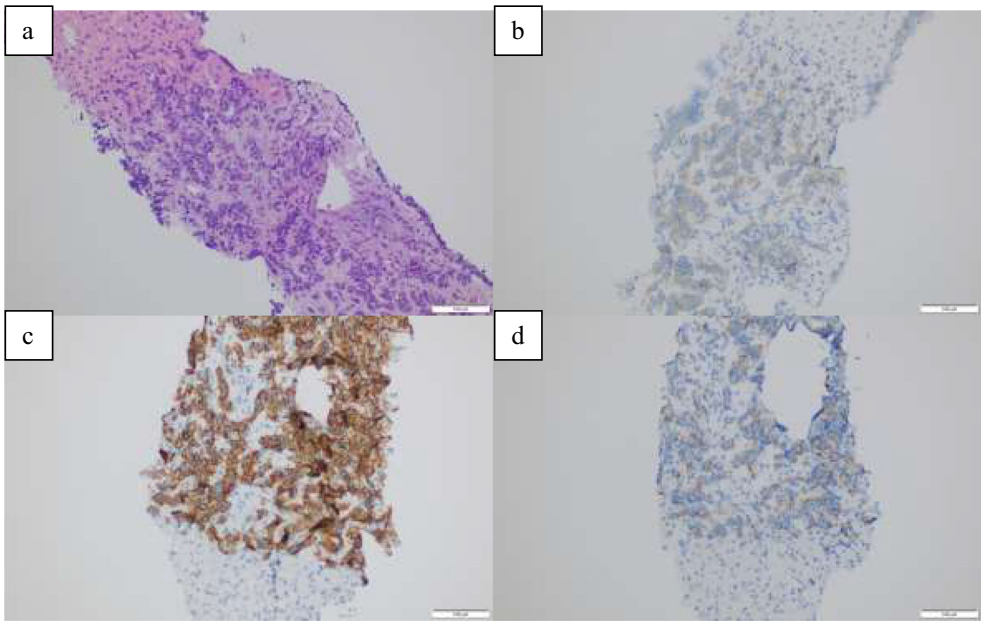

Fig. 3 Patient N°10, hepatic biopsy, HE (**a**), synaptophysin (**b**), CD56 (**c**) and chromogranine (**d**) staining. The density of the different neuroendocrine markers may vary

present upon diagnosis of de novo prostate cancer [2, 3] (Fig. 1).

The pathological characteristics of neuroendocrine tumours are the staining with immunohistochemical markers (CD 56, synaptophysin, chromogranin A, NSE), high proliferative rate (Ki67 > 50%) and the presence of TMPRSS2-ERG rearrangement [2]. Synaptophysin is the most sensitive marker, NSE is also sensitive but not specific, chromogranine is the most specific marker [2] (Fig. 3). The oncogene n-myc is considered as a driver of the progression of neuroendocrine prostate cancers. Aurora kinase A is a cofactor that stabilises n-myc [7]. The possible positivity of TTF1+ may be a confounding element [3].

Considering the possibility of rapid diagnosis, the easiest although not specific test upon suspicion of neuroendocrine differentiation of a prostate cancer is the determination of serum NSE level.

Considering other therapeutic options, the analogues of somatostatin are only indicated in low or intermediate grade neuroendocrine tumours (Ki67 < 10%) that are especially rare in the prostate. A phase II study supports the potential efficacy of the Aurora kinase A inhibitor alisertib in neuroendocrine prostate cancers [7]. Other propositions are the PARP1 inhibitors [8].

Conclusions

The incidence of neuroendocrine tumours among prostate cancer patients was higher than expected. Some of the patients had a relatively good outcome.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflict of interest in connection with the publication of this article.

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