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SHORT COMMUNICATION

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Primary mosaic neuroendocrine/adenocarcinoma of the prostate

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Abstract

Mosaic cancers are composed of two or several genetically different cell populations. Mosaicism has been considered to be rare among solid malignancies, with the exception of the germ cell tumours. Although neuroendocrine foci have been described within adenocarcinomas of the prostate, they have been interpreted as an advanced stage of the disease and the clinical relevance of the histological finding has remained uncertain. In this communication we give a summary on neuroendocrine prostate cancers. We recall the results of a recent single centre cohort of patients with neuroendocrine prostate cancer that showed higher incidence and better prognosis as expected by the literature. We show for the first time histological images of a primary mosaic neuroendocrine/adenocarcinoma of the prostate. A model explaining the development of mosaic cancers in the prostate is presented. Finally, we discuss the phenomenon of mosaicism related to prostate cancer in general.

Keywords

Neuroendocrine; Mosaic; Mosaicism; Prostate cancer; Immunohistochemistry

1. Mosaicism

Mosaicism is defined as the presence of two or several genomes in an individual or a tissue. Everyone acquires multitudes of genomic mutations during development, growth and aging despite having efficacious DNA repair mechanisms. Earlier these somatic mutations were poorly explored; however, new generation sequencing technologies have allowed the more precise characterisation of somatic mosaicism. The number of mutations increases with aging and so increases the risk of developing malignant transformations [1].

Mosaicism may appear in three different contexts: within a healthy organ, within a cancerous organ and within a cancer itself. Within a healthy organ the multiplication of a cell that has undergone somatic mutation may lead to the formation of mosaic tissue. Cancer cells usually hamper multiple mutations and their multiplication is more rapid compared to the surrounding tissue, so literally every cancerous organ is mosaic. When cancer cells alter further they may form a mosaic cancer [2].

Heterogeneity is a more frequently used and broader term for expressing irregularity of cancers. Beyond genetic differences it refers to epigenetic modifications and also to microenvironmental influences including the pattern of tumour infiltrating immune cells, endothelial cells and stromal cells [3]. The issue of the investigation of cancer heterogeneities would be the identification of therapeutically targetable alterations; hence heterogeneity of cancers has got limited clinical impact so far.

The particularity of prostate cancer is that in most cases it appears to be multifocal and plurimorphic [4]. This means that it may have several synchronous individual localisations and within a single laesion as well as between laesions the cells may show morphologic variability. The topographic heterogeneity explains the necessity of doing cartographic sampling and the morphologic heterogeneity has been recognised for a long time in the Gleason grading system used in the histopathological reports. The Gleason score correlates with the clinical prognosis. Intratumoral heterogeneity can be identified even within single primary tumour foci by whole genome sequencing [5].

Sequencing studies suggest that the clonal diversity is higher within primary tumours than in metastatic samples. Indeed, the more complex the diversity of a primary tumour the higher is the rate of recurrence [4]. Among the multiple clonal varieties only a limited number seem to be capable to form metastases. Therefore, in the metastases of untreated patients the heterogeneity may be lower than in their primary tumours.

Whole exome profiling realised on prostatectomy and pelvic lymph node samples of the same patients found that 87% of the subclones detected in the regional lymph node metastases were genetically related to the primary tumour of the same patient [5].

For distant metastatic prostate cancer the rule is that while initially the disease usually responds to androgen deprivation therapy it becomes castration resistant with time. The resistance mechanisms are subject of intense investigations.

2. Neuroendocrine prostate cancer

Neuroendocrine prostate cancer (NEPC) is considered to be the worst prognostic form of metastatic castration resistant prostate cancer. In some autopsy cohorts the prevalence of NEPC in metastatic castration resistant prostate cancers has been described in up to 20% [4]. However, in the clinical routine the prevalence of NEPC is found to be much lower. In a Surveillance, Epidemiology and End Results (SEER) database report the incidence of NEPC was only 0.04% among all prostate cancer patients [6]. This frequency certainly does not explain the resistance mechanism of the majority of the cases.

Considering the development of NEPC the current hypothesis is that it evolves from a preexisting adenocarcinoma by dedifferentiation under androgen deprivation therapy [4]. Thus, it is assumed to represent a late stage of the disease.

Neuroendocrine cells are normally present in the prostatic tissue [7]. Due to their isolation and rarity their identification in the normal tissue by hematoxylin-eosin staining remains extremely challenging [8]. NEPC may present as small cell or large cell carcinoma. Carcinoid tumours have only rarely been described [9]. Similarly to adenocarcinoma in normal prostatic tissue NEPC may also develop in adenocarcinoma in single or multiple foci. *De novo* NEPC has also been recognised [9] but only in homogenous small cell cancer like form.

Neuroendocrine cancers may be identified by specific immunohistochemistry (IHC) stainings with synaptophysin, cluster of differentiation 56 (CD56) or chromogranine A. The suspicion of NEPC may be supported if one of the two tumour markers, neuron specific enolase (NSE) and chromogranine A is detected at elevated level [4].

A recent prospective single centre cohort of patients with NEPC showed higher incidence and better prognosis as expected by the literature [10]. 10 prostate cancer patients out of a total of 521 showed neuroendocrine phenomena, so the clinical incidence was over 2%. 5 patients' survival reached one year, the longest survivor lived over 5 years. 3 patients received 3 lines of palliative chemotherapy. A patient with localised disease underwent prostatectomy after neoadjuvant chemotherapy and was lost of an intercurrent disease without having signs of relapse. Interestingly, patients with favorable outcome had dual elevation of the tumour markers prostate specific antigen (PSA) and neuron specific enolase (NSE) and responded to both anticancer treatments (those usually directed for prostatic adenocarcinoma and those for high grade neuroendocrine cancer) administered in an alternating way.

In this study the neuroendocrine phenomena were tested by IHC (synaptophysin, CD56, chromogranine A) and laboratory chemistry (NSE, chromogranine A) when clinicians suspected the diagnosis. The diagnosis of neuroendocrine cancer was established in two cases: (1) either by a positive IHC staining with neuroendocrine markers (2) or by the observation of a favourable radiologic response of a metastatic disease to platinum-based chemotherapy expressed also by the decrease of elevated neuroendocrine serum markers (Table 1).

The local study was closed at the end of 2018. We have still been diagnosing NEPC in about 2% of all prostate cancer cases and have been having patients with relatively good outcome. We published case reports presenting the pitfalls of the diagnosis and the possibility of several years of survival [11]. Some of our metastatic mosaic neuroendocrine/adenocarcinoma patients did not have androgen deprivation therapy or only for a short period of time. Therefore, we formulated a doubt on the current concept that explains the formation of NEPC with long lasting anti-hormonal treatment.

3. Primary mosaic neuroendocrine/adenocarcinoma of the prostate

Here we show—to our knowledge for the first time—images of primary mosaic neuroendocrine/adenocarcinoma of the prostate. The presented superposed images were realised with the Inkscapevektographic drawing software. The lower layer was the hematoxylin-eosin stained (Merck reagent) in normal mode, the upper layer was the chromogranine A stained (Cell Marque LK2H10, DakoAutostainer, Rocklin, CA, USA) in darken mode.

Fig. 1 represents isolated neuroendocrine cells within an acinar adenocarcinoma (Gleason grade group 3) in a prostate biopsy specimen. The density of the neuroendocrine cells is not higher in the cancer than in the normal prostatic tissue. However, it cannot be excluded that one of them might be the source of a malignant neuroendocrine line. The patient received 74 Gy of radiotherapy to the prostate. A year later he was diagnosed in another hospital with intermediate grade neuroendocrine cancer affecting paraaortic lymph nodes and the liver, localisations of predilection for metastatic NEPC. Since no primary tumour was found the suspicion that the earlier diagnosed prostate cancer be the origin may be raised.

Fig. 2a represents a primary prostate cancer (Gleason grade group 5). Fig. 2b shows positivity of chromogranine A IHC staining. Fig. 2c is the superposition of the two above figures showing clearly that only a part of the malignant cells are stained and thus have neuroendocrine feature. The remaining part is common adenocarcinoma. This figure demonstrates a primary mosaic prostate cancer. The patient underwent prostatectomy after receiving 3 cycles of primary cisplatin-

TABLE 1. Diagnostic criteria of the neuroendocrine cancer of the prostate.

Diagnostic criteria of the neuroendocrine cancer of the prostate
Major: positive IHC staining with either CD56, synaptophysin, chromogranine A or NSE
Minor: elevation of serum NSE or chromogranine A
Minor: favourable response to a platinum-based chemotherapy

One major or two minor criteria are needed for the retention of the diagnosis. IHC: immunohistochemistry; NSE: neuron specific enolase; CD56: cluster of differentiation 56.

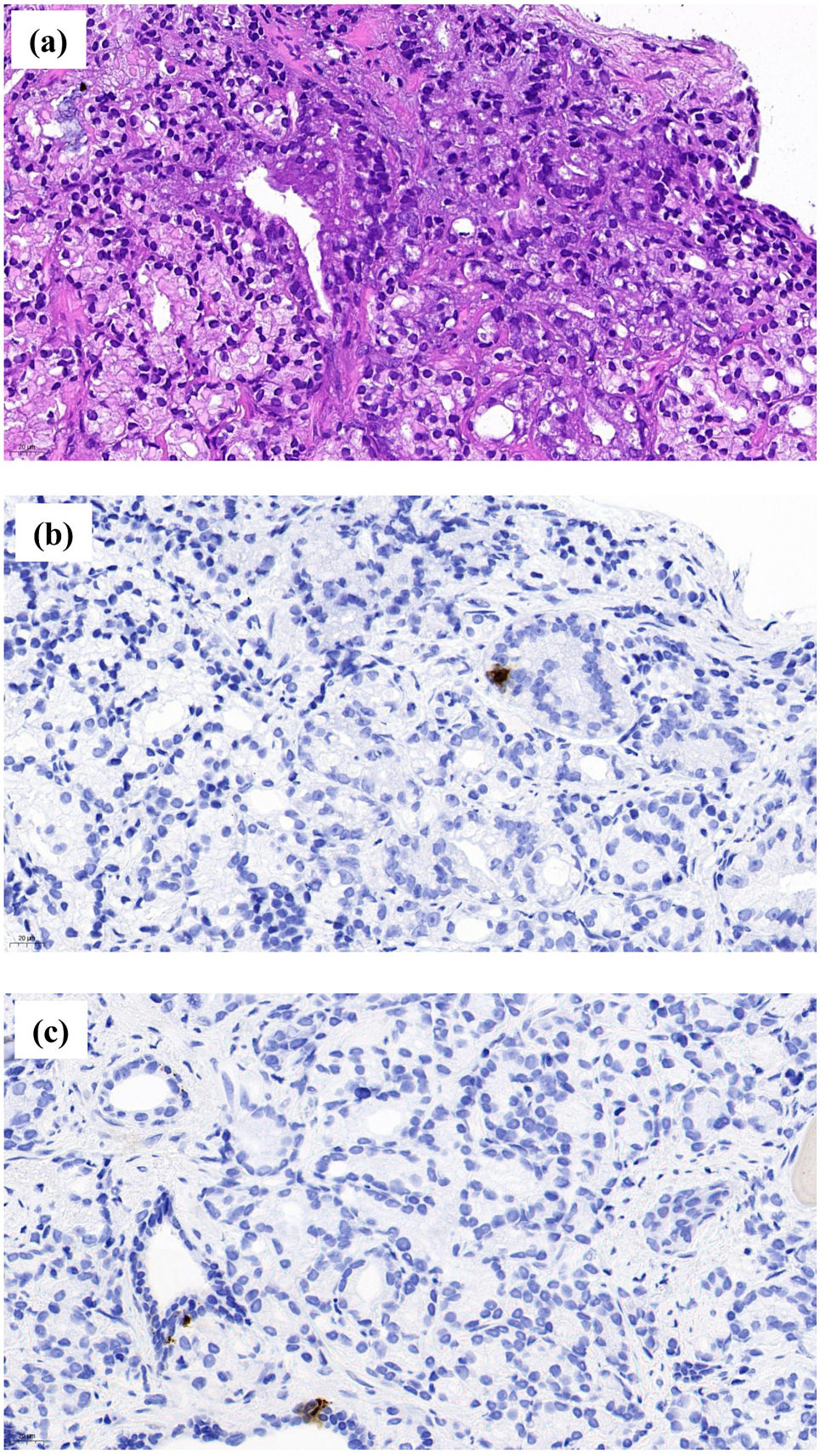

FIGURE 1. Biopsy specimen of a prostatic acinar adenocarcinoma. (a) Haematoxylin-eosin staining. (b) Chromogranine A immunohistochemistry showing a positive cell in the malignant zone. (c) Chromogranine A immunohistochemistry showing two positive cells in the normal glandular zone (The scale bars show 50 μm).

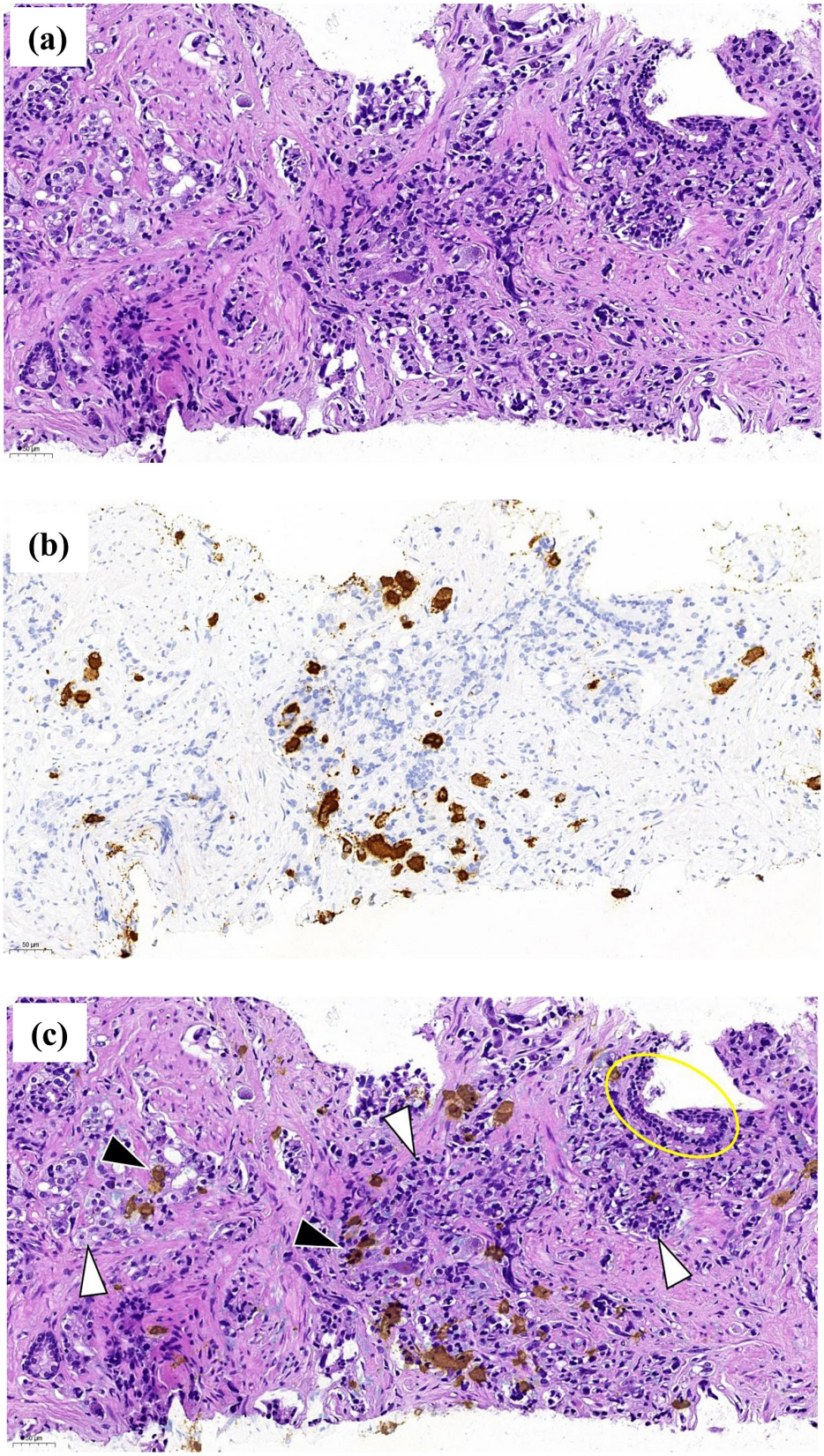

FIGURE 2. Biopsy specimen of a prostatic mosaic neuroendocrine/adenocarcinoma. (a) Haematoxylin-eosin staining. (b) Chromogranine A immunohistochemistry showing numerous positive cells in the malignant zone. (c) Superposition of Fig. 2a,b. Δ showing malignant adenocarcinoma cells, ▲ showing neuroendocrine cells, the yellow circle showing a normal glandular zone. (There are also necrotic zones staining with chromogranine A, *e.g.*, at the bottom in the middle of the slide. The scale bars show 50 μm.).

etoposide treatment. The prostate did not show any positivity at neuroendocrine IHC, meaning that the neuroendocrine component was in complete pathological remission after cytotoxic therapy. 22 months after prostatectomy, definitive radiotherapy of the prostatic bed was realised for biochemical relapse. Prostate specific membrane antigen positron emission tomography/computed tomography (PSMA PET-CT) showed only local hyperfixation.

While the parallel presence of neuroendocrine carcinoma and adenocarcinoma can only be speculated on the first sample it is clearly documented on the second one. It is not difficult to imagine that in the absence of preoperative chemotherapy and prostatectomy the disease would have become metastatic and it may also be suspected that the two parts might show different progression rate and also different spreading localisations.

4. A model for the development of mosaic prostate cancers

Currently, the most efforts of prostate cancer research are concentrated to the understanding of mechanisms of resistance to castration. The problematic of the pathogenesis of NEPC is part of these investigations. Some authors propose the divergent evolution of NEPC from one or more adenocarcinoma cells, based on results of extensive whole exome sequencing [12]. NEPC is the sui generis castration resistant cancer. As mentioned earlier it is usually observed in late stage of the disease and is generally suspected to arise by dedifferentiation under long lasting androgen deprivation therapy [13]. A review published in this Journal recognises the possibility that neuroendocrine differentiation may appear in earlier stage of the disease but also supports the hypothesis that adenocarcinoma cells are the precursors of the malignant neuroendocrine cells [14]. Contrarily to these theories, our findings suggest the possibility of parallel evolution of the two components from the onset on.

For supporting our explanation, we rely on the works of Blackwood *et al*. [15]. They demonstrated (through the observation of the transmission of changes in the mitochondrial DNA) that different cells of the normal prostatic epithelium originate from a common epithelial stem cell. With other words, an epithelial stem cell may supply the whole cellular population of the acini, *i.e.*, basal cells, luminal cells and neuroendocrine cells as well.

Although according to the current concept prostate cancer stem cells are among the luminal cells [16] with the above model it is enough to assume that prostate cancer may also arise from epithelial stem cells to explain the parallel development of adenocarcinoma and neuroendocrine cancer. The observation that the prostate cancer specific transmebrane protease, serin 2-erythroblast transformation-specific related gene (TMPRSS2-ERG) rearrangement is similarly present in 50% in adenocarcinomas as well as in neuroendocrine carcinomas further supports the hypothesis of shared clonal origin [17]. Similarly to non-seminomatous germ cell tumours [18] and chronic myeloid leukaemia the proliferation of a malignant-turned stem cell could be responsible of the mosaic pattern.

Furthermore, mosaicism could explain some of the otherwise not evident observations related to the hormone sensitivity of prostate cancers. Since the introduction of second line antihormonal therapies their optimal use has not been established. (We prefer using the term “second line” or “androgen receptor signalling inhibitors” instead of the generally applied androgen receptor targeted agents abbreviated for “ARTA” as we find these ones less misleading. Please, consider that there are medications that act on the androgen receptors still they are not considered among ARTAs and contrarily, not all ARTAs act on the androgen receptors.)

First, subsequent studies showed that the more anticancer drugs were used in parallel from the beginning on for the treatment of a hormone sensitive metastatic prostate cancer the more additional clinical benefit could be obtained [19, 20]. Second, administration of the second line antihormonal agents is recommended until clinical or radiological progression. Or, in a small set of patients of our single centre, patients whose treatment was stopped at PSA progression did not have a worse prognosis than those treated several months longer until clinical or radiological progression [21]. In addition, the same antiandrogenic drug was reintroduced to some patients after progression under second line chemotherapy by cabazitaxel. A novel decrease in PSA level could be observed in patients treated earlier until PSA progression as well as until radiological progression (yet unpublished data). It means that in these patients the cancer lost its earlier gained resistance to the antihormonal drug. The most plausible explanation for this unexpected phenomenon would be the parallel presence of different cell lines.

Let’s admit that adenocarcinoma cells of different characteristics may arise from a single malignant-turned stem cell. Even if these cells have the same phenotype they may differ in terms of their mechanism of resistance to androgen deprivation. In this case a treatment line may suppress one cell line more than the other. Parallel use of the treatments may suppress more cell lines. Sequential use of the treatments may block a cell line that was not suppressed by the preceding treatment. The deductions of the hypothesis correspond exactly to the clinical observations.

Concerning the reasons for missing the right diagnosis of NEPC in the clinical routine, the two main reasons are the rarity of neuroendocrine IHC staining on biopsy samples either of the prostate or the metastatic laesions (Table 2), and the erroneous elimination of the potential prostatic origin for a metastatic disease progression on the basis of a non-elevated PSA level. Repeating the biopsy of the prostate for a known prostate cancer patient is uncommon. Similarly, sampling metastatic sites particularly in the bone is not the rule. Making neuroendocrine IHC staining for an adenocarcinoma of unknown primary is not part of the clinical routine either. Relying on biomarkers is no more evident. NSE is sensitive but not specific. Chromogranine A may be difficult to access in certain laboratories. Strategies to improve the detection rate of neuroendocrine prostate cancers are summarised in Table 3.

One of the reasons why NEPC has not been in the focus of clinical interest may be that therapeutic options used to be limited to platinum-based chemotherapy. Some recent investigations have promising results. Aurora kinase A (AURKA) and N-myc have been identified as potential drug targets [17]. Dual AURKA and N-myc inhibitors developed by structure-

TABLE 2. Clinical situations when neuroendocrine cancer of the prostate should be suspected.

Clinical situations when neuroendocrine cancer of the prostate should be suspected
Clinical or radiological progression of prostate cancer without PSA rise
Diagnosis of an extended metastatic disease associated to a relatively low PSA
Presence of any non-pulmonary visceral metastases
Metastatic carcinoma of unknown primary

PSA: prostate specific antigen.

TABLE 3. Strategies to improve the detection rate of neuroendocrine prostate cancers.

Strategies to improve the detection rate of neuroendocrine prostate cancers
Avoiding to consider PSA as unique and to 100% sensitive marker of prostate cancer
Realisation of neuroendocrine IHC staining in the situations summarised in Table 2.
Determination of NSE and/or chromogranine A when biopsy or IHC are not feasible

IHC: immunohistochemistry; NSE: neuron specific enolase, PSA: prostate specific antigen.

based drug design are under *in vitro* testing [22]. ^{177}Lu-PSMA-617 was approved in the last year for the treatment of PSMA-positive castration resistant prostate cancer. It may be efficacious not only in adenocarcinomas but also in NEPC, because some neuroendocrine cancers show PSMA-positivity [23]. Furthermore, in mosaic cancers it may be bound by PSMA-positive adenocarcinoma cells and act also on PSMA-negative neuroendocrine cells in proximity.

Concerning ongoing investigations on prostate cancer development it may be suspected that the androgen receptor pathway plays not the only and maybe not even the major role. A study that analysed prostate cancer patients' urinary microbiome and primary prostate cancer histology found correlation between presence of bacteria in the urine sediment and prostate cancer risk groups. They identified four novel bacterial species. Furthermore, they identified five anaerobic bacteria which included three of the novel isolates that were associated with higher cancer risk groups [24].

Mosaicism and prostate cancer have another interesting common point. Mosaic loss of Y chromosome in white blood cells is a frequent alteration in aging men. An increased risk of prostate cancer has been shown in men of European and East Asian origin carrying loss of chromosome Y [25].

Concerning the incidence of neuroendocrine cancers arising in different organsit is interesting to note that it is not homogenous. The highest incidence may be found in the gastrointestinal tract and in the pancreas. Although most of these cancers are less aggressive as compared to NEPC, the current clinical practice guideline of the European Society for Medical Oncology recognises mixed gastroentero-pancreatic neuroendocrine neoplasias [26].

Finally, for those who find the term "primary mosaic neuroendocrine/adenocarcinoma of the prostate" to be too complicated and in addition like word games we propose the denomination of Petz NEPC.

5. Conclusions

Neuroendocrine prostate cancer is underdiagnosed in the clinical routine and its prognosis is underestimated. We presented a case of primary mosaic neuroendocrine/adenocarcinoma of the prostate. This entity underlines the importance of mosaicism in the pathogenesis of prostate cancer.

AVAILABILITY OF DATA AND MATERIALS

The main data are presented within this article. Further source data are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

KA—identified the primary mosaic neuroendocrine/adenocarcinoma of the prostate; prepared the figures. TK—wrote the first version of the text. KA and NK—gave their remarks and made corrections. All authors have read and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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