



# *De novo* purely prostatic large-cell neuroendocrine carcinoma with thyroid and adrenal metastases

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## Summary

Large-cell neuroendocrine carcinoma (LCNEC) is a rare neuroendocrine prostatic malignancy. It usually arises after androgen deprivation therapy (ADT), while *de novo* cases are even more infrequent, with only six cases described. The patient was a 78-year-old man with no history of ADT who presented with cervical lymphadenopathy. Diagnostic approaches included PET/CT, MRI, CT scans, ultrasonography, biopsies, and cytological and immunohistochemical evaluations. Results showed a poorly differentiated carcinoma in the thyroid gland accompanied by cervical lymph node enlargement. Thyroid surgery revealed LCNEC metastasis to the thyroid gland. Additional metastases were identified in both the adrenal glands. Despite appropriate treatment, the patient died of the disease. *De novo* LCNEC of the prostate is a rare, highly aggressive tumor with a poor prognosis. It is resistant to most therapeutic agents, has a high metastatic potential, and is usually diagnosed at an advanced stage. Further studies are required to characterize this tumor.

## Learning points:

- *De novo* LCNECs of the prostate gland can metastasize almost anywhere in the body, including the thyroid and adrenal glands.
- LCNECs of the prostate are usually associated with androgen-depriving therapy, but *de novo* cases are also notable and should be accounted for.
- Further studies are required to fully understand and treat LCNECs more effectively.

## Background

The presented case depicts the diagnostic and therapeutic management of one of the most rarest and lethal neoplasms of the prostate gland. Only six similar cases have been described in the global literature and none had adrenal or thyroid metastases, thus making the diagnostic approach an extremely challenging task.

## Case presentation

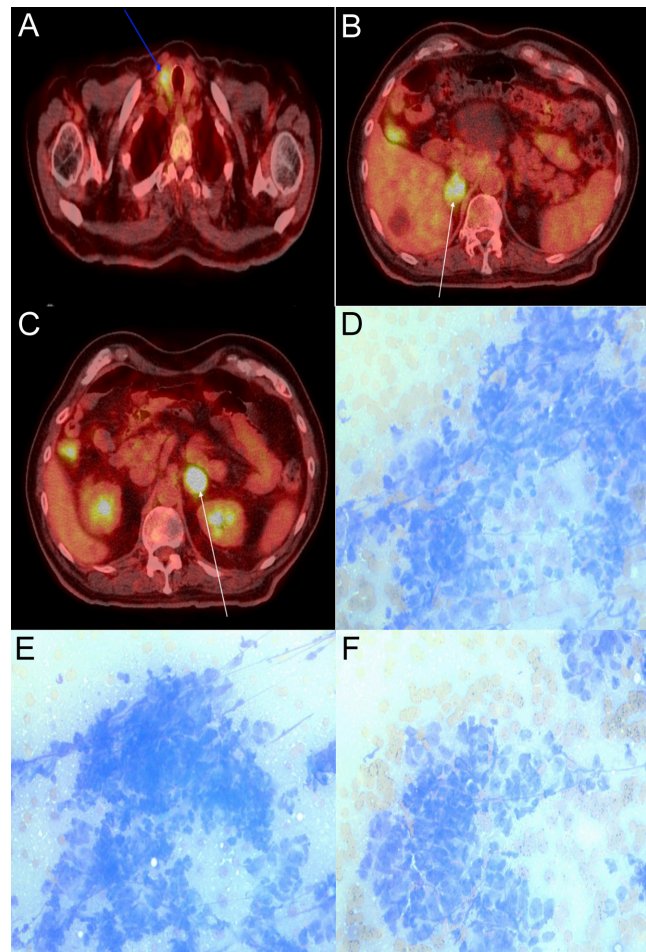
A 78-year-old man presented to the emergency room (ER) of a rural Greek hospital complaining of a lump on the side of his neck. His medical history was remarkable for back pain for more than 10 years, laparoscopic cholecystectomy 23 years ago, past tobacco use (20 pack-years), and benign prostate hyperplasia (BPH), for which he was receiving no

treatment. Physical examination revealed a body weight of 84 kg, height of 184 cm, painless, unilateral, supraclavicular lymphadenopathy, facial rubor, and a mild ‘moon face’ demonstration.

## Investigation

At the time of presentation, fine-needle aspiration (FNA) of the enlarged lymph node was performed and revealed findings compatible with low-differentiation malignancy of unknown origin, but the cytological findings are unfortunately not available. CT of the cervical, thoracic, upper, and lower abdominal regions revealed pathologically enlarged supraclavicular, mediastinal, para-aortic (distal part), and iliac lymph nodes with shapes indicative of metastatic infiltration, as well as a non-enriching region on the right lobe of the thyroid gland. The prostate (6.5 × 7.4 cm) and both adrenal glands (left: 2.4 cm, right: 1.4 cm) were enlarged and the patient was referred to our referral private hospital in Athens, Greece, for further evaluation and treatment.

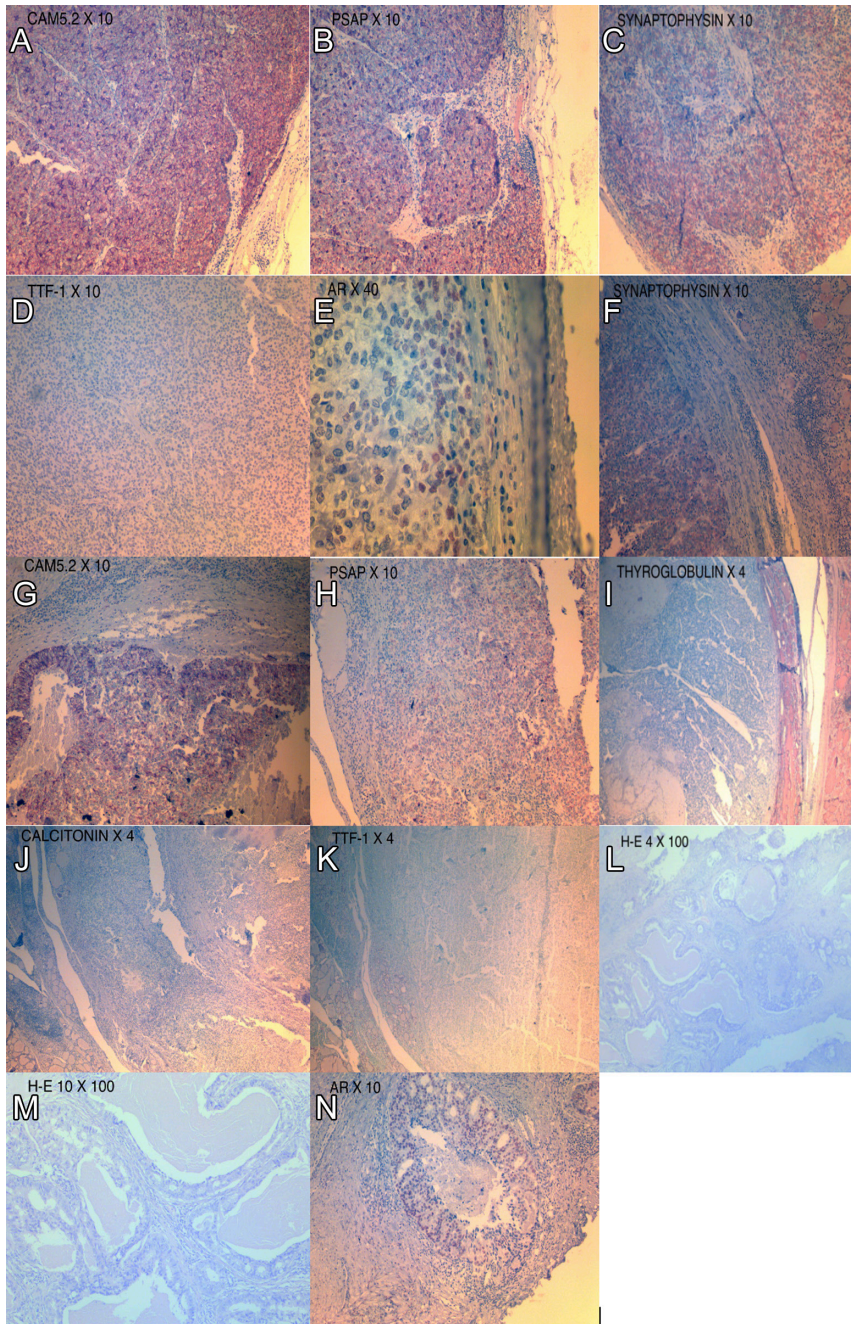
PET/CT with 18F-fluorodeoxyglucose was performed on arrival. Increased uptake was found in all the above-mentioned areas, including both adrenal glands and the thyroid (Fig. 1A), as well as in the patient’s axilla, perihepatic, and peripancreatic regions, and the left half of the sacral bone. A digital rectal examination was performed and showed an enlarged prostate gland with a smooth surface. The patient’s prostate-specific antigen (PSA) was 6.5 ng/mL. According to Catalona *et al.*, only 22% of patients with PSA levels between 4.0 and 9.9 ng/mL were eventually diagnosed with prostate cancer; therefore, the possibility of a PSA-negative tumor became much more likely (1). Subsequently, the patient underwent a fine-needle biopsy (FNB) of the prostate gland, which identified a highly malignant, diffuse, poorly differentiated prostatic adenocarcinoma with a Gleason score of 9 (5+4) and grade group 5 in multiple regions, accompanied by dense chronic inflammation and cancerous perineural infiltrations. The specimen stained positive for synaptophysin but not for thyroid transcription factor-1 (TTF-1). FNB was followed by neck ultrasonography (U/S), which confirmed the presence of enlarged cervical lymph nodes with the addition of two hypoechoic regions on the right lobe. FNA of the thyroid nodule was performed and presented findings consistent with a poorly differentiated carcinoma (Bethesda classification: 6, based on the finding of marked atypia of medium-sized cells with limited protoplasm and strongly hyperchromatic nuclei with prominent nucleoli, organized in dense accumulations (Fig. 1D, E and F).



**Figure 1**

Axial plane PET/CT scans and thyroid FNA specimen examination. (A) PET/CT exhibiting a hypermetabolic region located on the right thyroid lobe with a maximum standardized uptake value (SUVmax) of 5.2 (blue arrow), confirming the presence of active disease involving the thyroid gland. (B and C) Confirmatory PET/CT revealing increased 18F-FDG uptake throughout both adrenal glands (white arrows, B: right adrenal gland, C: left adrenal gland) with a SUVmax of 6.3 on the right and 12 on the left. Both the diameter and FDG uptake increased in comparison to the previous PET/CT, indicating disease progression. (D, E and F) Cytological imaging of the thyroid FNA specimens. The specimen was characterized by medium-sized cells with limited protoplasm and strongly hyperchromatic nuclei with prominent nucleoli organized in dense accumulations when stained with Giemsa. Immunohistochemical staining was not performed on this specimen. These findings were consistent with poorly differentiated adenocarcinomas of prostatic origin.

Considering the symptoms of dysphagia and in accordance with the patient’s wishes, a palliative total thyroidectomy with central and bilateral lymph node dissection was performed. Along with the thyroid gland, 12 lymph nodes from the central compartment and 10 lymph nodes from the right lateral cervical compartment were identified on histological evaluation (Fig. 2A, B, C and D). Pathological examination of the



**Figure 2**

Pathological images from cervical lymph node resection, total thyroidectomy, and transurethral prostatectomy specimens. (A, B, C and D) Lymph nodes resected from the right lateral cervical region. In this specimen, the observed cells were positive for CAM 5.2 (A), PSAP (B), and synaptophysin (C) but negative for TTF-1 (D), ruling out the thyroid origin of the tumor. All images were magnified 10 $\times$ . (E, F, G, H, I, J and K) Samples from total thyroidectomy. Pathological evaluation indicated that large cells had invaded the thyroid capsule and local blood vessels. They were typified by abundant cytoplasm, pleomorphic nuclei with either diffuse chromatin or prominent nucleoli arranged in lobular structures, and necrosis. The cells were positive for AR (E, magnified 40 $\times$ ), synaptophysin (F, magnified 10 $\times$ ), CAM 5.2 (G, magnified 10 $\times$ ), PSAP (H, magnified 10 $\times$ ), and negative for thyroglobulin (I, magnified 4 $\times$ ), calcitonin (J, magnified 4 $\times$ ), and TTF-1 (K, magnified 4 $\times$ ). These findings are incompatible with those of primary thyroid neoplasms. (L, M and N) Transurethral prostatectomy surgical specimens. With eosin-hematoxylin staining (L, 4  $\times$  100 and M, 10  $\times$  100 magnification), pathologic examination revealed medium-sized cells with pleomorphic nuclei characterized either by diffuse chromatin or prominent nucleoli and central necrotic cores. The cells were organized into lobular accumulations and infiltrated multiple regions of the gland. In IHC staining, the cells stained positive for AR (N, 10 $\times$  magnification).

thyroid specimen was consistent with a highly cellular tumor with large cells, abundant cytoplasm, and pleomorphic nuclei with either diffuse chromatin or prominent nucleoli, arranged in lobular structures, and necrosis. The cells invaded the thyroid capsule and local blood vessels. Immunohistochemistry (IHC) analysis revealed that the tumor was positive for AR (Fig. 2E), synaptophysin (Fig. 2F), CAM5.2 (Fig. 2G), prostate-specific acid phosphatase (PSAP) (Fig. 2H), CK8.18, and partially positive for alpha-methylacyl-CoA racemase

(AMACR), while it was negative for thyroglobulin (Fig. 2I), calcitonin (Fig. 2J), TTF-1 (Fig. 2K), PSA, CD56, NSE, and keratin-903. 30% of the cells studied were positive for Ki-67 and chromogranin. The absence of thyroid-related markers ruled out the possibility of a primary thyroid neoplasm. A few days later, the patient underwent transurethral prostatectomy, and histological evaluation of the surgical specimen revealed the presence of malignant infiltrations in multiple regions of the gland organized in lobular accumulations. The



observed cells were medium-sized, with pleomorphic nuclei characterized by diffuse chromatin or prominent nucleoli. Central necrotic cores were also present (Fig. 2L and M). IHC analysis revealed that the cells stained positive for CAM5.2, synaptophysin, and PSAP, partially positive for AMACR and negative for PSA, keratin 903, and TTF-1. The tumor cells also stained strongly positive for androgen receptor (AR) (Fig. 2N). Considering these findings, we diagnosed a *de novo* prostatic large-cell neuroendocrine carcinoma with thyroid metastasis.

## Treatment

In accordance with the immunophenotype of the tumor, the therapeutic approach consisted of a dual-regimen androgen deprivation therapy with bicalutamide and a luteinizing hormone-releasing hormone analog, along with four cycles of systemic chemotherapy with paclitaxel and carboplatin. In the following 2 months, CT and MRI of the abdominal and thoracic cavities were consistent with a partial response; infiltrated lymph nodes shrank and no additional metastatic lesions arose. Unfortunately, 3 months after the initiation of treatment, follow-up MRI of the abdomen revealed further enlargement of both adrenal glands and the presence of spinal intraosseous lesions compatible with metastatic disease. Confirmatory PET/CTGa68-DOTATATE (Fig. 1B and C) revealed disseminated metastatic disease in these areas. The therapeutic regimen was then changed to carboplatin and etoposide.

## Outcome and follow-up

One month later, the U/S of the bladder and prostate were indicative of irregular distension of the posterior wall of the urinary bladder. A transurethral resection was performed, and the examination of a surgical specimen from the bladder neck revealed large cells with abundant protoplasm, pleomorphic nuclei with diffuse chromatin and prominent nucleoli, and increased mitotic activity, organized in lobular structures. In the IHC assessment, cells stained positive for synaptophysin, CAM5.2, and PSAP, while they were negative for human melanoma Black-45 (HMB-45) and TTF-1. Ki-67 was expressed in 50–60% of the observed cells. The cytological and IHC results were compatible with metastatic infiltration of the bladder neck by LCNEC cells. The therapy was once again changed to topotecan. After four cycles, the patient presented with macroscopic hematuria. He succumbed to metastatic disease a few days later.

## Discussion

The benign prostate epithelium consists of secretory luminal, basal, and neuroendocrine (NE) cells. NE (or endocrine-paracrine) cells in the prostate were first described by Pretl in 1944 (2) and are present in multiple other tissues, but the prostate gland harbors the greatest number by far, which is the cause of the high frequency of neuroendocrine differentiation in prostate cancer (2). These cells play an important role in the proliferative and secretory functions of the gland and are considered terminally differentiated; they are derived from a putative stem cell with a basal cell phenotype (3). The most common appearance of NE tumors is focal differentiation of conventional prostate adenocarcinomas (pCa). The coexistence of pure NE neoplasms with pCa is uncommon; however, coexistence with *de novo* NEPCs is much rarer. Their origin is associated with poorer prognosis, as most NEPCs do not express androgen receptors and are resistant to hormonal therapy (2). LCNEC is the rarest form of NEPC with increasing numbers of NE cells; therefore, its development is believed to be associated with ADT in patients with pCa (4). Our patient had no history of ADT or conventional pCa and no remarkable risk factors explaining this unique nosological entity or its metastatic behavior. Therefore, the tumor was considered a purely *de novo* neuroendocrine cancer of the prostate gland. In the past, several cases of prostate adenocarcinoma metastasis to the thyroid gland have been described in autopsy series (5) and far fewer in case reports (6). In addition, an extremely rare case of cervical lymph node metastases arising from an NE pCa without metastasis to the thyroid gland, but the coexistence of papillary microcarcinoma of the thyroid, has been described (7). In our patient, the definitive diagnosis was made only after the tumor, and the thyroid metastases were biopsied. Typically, by the time patients seek medical attention, the disease is extensive with metastasis and lymphadenopathy (8).

Contrary to the rarity of metastases to the thyroid gland, a prevalence of 12.8% for prostate-derived metastases to the adrenals has been described in an autopsy series of 1589 cases of prostate adenocarcinomas from Switzerland (5). Unfortunately, that study was published long before the recognition of neuroendocrine prostate carcinoma as a separate entity; thus, it was unable to provide statistics on that tumor. Therefore, despite the high likelihood of adrenal metastases from prostate neuroendocrine carcinomas, our case is the first to present these, in addition to being the first to describe thyroid metastasis from the same tumor.



#### Declaration of interest

R D Paparodis is a Senior Editor of *Endocrinology, Diabetes, and Metabolism Case Reports* and was not involved in the review or editorial process for this paper on which he is listed as an author. The other authors have no relevant financial, non-financial, or competing interests to declare.

#### Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

#### Patient consent

Both consent to publish the figures and consent to participation were acquired in written form prior to the patient's demise.

#### Author contribution statement

E Karvounis was the patient's surgeon who performed thyroid and lymph node biopsies and excisions. In addition, he assisted with writing and revising the manuscript; RD Paparodis is an endocrinologist who provided guidance and supervision for the entire manuscript preparation process; I Zoupas is a medical student who collected clinical data and was primarily responsible for writing the initial draft; R Efthymiadou conducted the diagnostic imaging tests and captioned the PET-CT images included in the manuscript. In addition, she assisted with writing and revising the manuscript; D Bantouna is a pathologist who reviewed the diagnoses set by the care team and assisted in writing and revising the manuscript; C Ioakimidou is a pathologist who examined histopathological specimens and delivered a definitive diagnosis; C Panopoulos was the patient's oncologist and responsible for the diagnostic and medical therapeutic management of the patient. In addition, he assisted with writing and revising the manuscript.

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Received in final form 18 August 2022

Accepted 21 September 2022