Neuroendocrine Prostate Cancer: Report of a Prostate Cancer Subtype with Atypical Metastatic Imaging and Clinical Findings

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ABSTRACT

Prostate cancer is the leading cause of malignancy in males, and the vast majority of cases consist of androgen-sensitive acinar adenocarcinoma. Multiple relatively rare subtypes of prostate malignancy have been described, including a neuroendocrine prostate cancer, which can arise in response to androgen-deprivation treatment in the setting of existing prostatic adenocarcinoma. Neuroendocrine prostate cancer is an uncommon subtype of prostatic cancer with a highly aggressive course and lack of distinguishing features on conventional imaging. We present a case of prostatic cancer which developed into neuroendocrine prostate cancer with atypical metastatic imaging appearance and describe characteristics that may suggest a histopathologic change from the original malignancy.

CASE REPORT

CASE REPORT

A 65-year-old male presented with weakness and acute kidney injury, found to have obstructive hydroureteronephrosis from a prostate mass and elevated prostate specific antigen (PSA) of 689 ng/mL (normal <4). He was diagnosed with prostate cancer, and initial iliac bone biopsy yielded metastatic prostate adenocarcinoma, positive for prostate-specific p501s marker. The patient began androgen deprivation therapy within two weeks. Initial staging workup revealed multiple sclerotic bone lesions (Figure 1).

Follow up imaging performed less than six months after diagnosis revealed new large lesions centered in the right third rib and the left twelfth rib (Figure 2), which were lytic with extensive surrounding soft tissue components. PSA at that time was 5 ng/mL. Repeat biopsy performed within a week reported large cell neuroendocrine carcinoma prostate with large necrotic portions, negative for p501s and prostate specific membrane antigen (PSMA), and with a high mitotic index with Ki-67 of 90%; unfortunately, the pathologic slides were not available to include with the present case report.

Subsequent imaging performed one month later for other clinical indications (evaluation for pulmonary embolism and nephrostomy tube placement) showed significant progression of the atypical bony metastatic lesions, in addition to numerous liver metastases (Figure 3), with PSA remaining at 5 ng/mL.

DISCUSSION

Etiology and demographics

Prostate cancer is the most common extra-cutaneous malignancy in males [1]. More than ninety percent of prostate malignancy are of the acinar adenocarcinoma subtype, which are androgen-driven tumors and often treated with androgen deprivation therapy [2-4]. However, multiple uncommon histologic variants exist [3], including neuroendocrine prostate cancer (NEPC), which makes up 0.5-2% [5-7] of prostate cancer cases. NEPC is the most lethal prostate malignancy subtype, with median survival of 9.8-13.1 months [8-9], 5-year overall survival of 12.6% [10], and distant metastases present at time of diagnosis in approximately half of patients [8-9]

NEPC can rarely originate from de novo mutations [5], but it more commonly arises in the course of evolving treatment resistance to androgen deprivation therapy; this setting is also termed castration-resistant prostate cancer (CRPC) [4,5]. As such, the typical androgen receptor signaling pathway is lost or dysregulated, and the classical correlation with prostate specific antigen (PSA) levels is often absent during progression of NEPC. In the case presented, PSA was substantially reduced following initiation of androgen deprivation therapy and remained low throughout the follow up period, despite the significant progression of NEPC.

Clinical and imaging findings

Imaging of NEPC, as with other prostate cancer subtypes, typically begins with ultrasound or MRI, and CT or PET-CT is more commonly used for staging purposes. There are no reliable distinct imaging features for NEPC compared to the more common prostate adenocarcinoma when utilizing conventional imaging, although additional PET imaging have been proposed to be beneficial; Gallium-68 with somatostatin analog (such as Ga-DOTATATE), often used in other neuroendocrine tumor imaging, has been shown to have high sensitivity and specificity for neuroendocrine type malignancies of the prostate [5,11]. Because NEPC often arises in the setting of CRPC with loss of the typical prostate biochemical signaling pathways, certain "prostate specific" imaging techniques such as PET with PSMA, may provide false negatives in these cases.

In this case, all initial findings were consistent with typical adenocarcinoma, including pathology with p501s marker, elevated PSA, and the typical sclerotic osseous metastases. However, the first follow up imaging had a notable change in the metastatic morphology; in addition to progression of the usual osseous metastases, there were two new lesions which were atypical in that they had predominantly lytic bony appearance and a large soft tissue extra-osseous component. These unusual findings prompted a second biopsy of the thoracic spine, which showed morphologic and immunophenotypical differences after pathologic review, including loss of the PSMA and p501s expression and a high mitotic index. The highly aggressive nature of this NEPC subtype was confirmed with significant enlargement of the atypical chest wall mass and numerous new hepatic metastases within the span of one month, which would also be highly atypical for prostate adenocarcinoma.

Treatment and prognosis

Treatment for NEPC currently employs chemotherapy regimens that have been studied for small cell lung cancer, which has similar neuroendocrine cell phenotype, typically with platinum-based therapies [12]. Combination with immune checkpoint inhibitors and novel biomarker targets are under investigation [13]. However, survival remains poor, with less than 50% response rate in typical platinum-based combination chemotherapy and less than 20% overall five-year survival [10, 12, 14].

DIFFERENTIAL DIAGNOSIS

Progression of prostate adenocarcinoma

In patients with known prostate adenocarcinoma, findings of metastatic disease are often presumed to represent progression of the original malignancy type. Supportive findings include increasing PSA levels and typical prostate adenocarcinoma metastatic pattern, including pelvic lymphadenopathy which sometimes presents as obstructive uropathy, potentially direct invasion of the bladder or rectal wall, and diffuse sclerotic osseous lesions. However, these features are not universal and ultimately pathologic correlation may be required to distinguish unusual findings of prostate adenocarcinoma spread.

Coexisting non-prostate malignancy

Aggressive metastatic lesions that appear after prostate cancer treatment initiation can also be seen in coexisting malignancies of a distinct origin. One notable example is lymphoma, with case reports of rapid progression following androgen deprivation therapy for prostate cancer, possibly from an enhanced estrogen mechanism [15]. The clinical and imaging appearance of non-prostate malignancies is highly variable. Conceptually, a co-existing non-prostate malignancy is a similar clinical scenario to NEPC, in which there has been differentiation from the original prostate adenocarcinoma into a pathologically distinct entity, and therefore biopsy confirmation is often required.

CONCLUSION

NEPC is a highly aggressive prostate malignancy with poor prognosis, which most often arises as a response to treatment resistance from prostate adenocarcinoma. Any imaging performed on patients with known or suspected prostate cancer should be scrutinized for abnormalities. Findings that do not fit the typical appearance for prostate adenocarcinoma spread (e.g. pelvic lymphadenopathy, bladder invasion, osseous sclerotic lesions) should be noted and closely followed to exclude atypical progression of disease. In such cases, clinical correlation with PSA and even prostate-targeting nuclear medicine scans such as PSMA-PET/CT may provide false negative information, and re-biopsy may be warranted. Future investigation for potential specific imaging findings and the utility of other imaging modalities, such as Ga-DOTATATE nuclear medicine imaging, may provide additional methods of detecting and monitoring this uncommon and highly aggressive malignancy.

TEACHING POINT

Neuroendocrine prostate cancer is an uncommon, aggressive prostate cancer subtype often arising after androgen deprivation therapy for prostate adenocarcinoma. Suspicious findings include aggressive metastatic progression with atypical features, such as lytic bone lesions and low PSA levels, and confirmation with tissue sampling is required to confirm the diagnosis.

AUTHORS' CONTRIBUTIONS

All authors contributed to the design and planning of the manuscript. Initial draft written by Bryan Nixon. All authors reviewed and agreed with the final version.

DISCLOSURES

The authors declare no financial disclosures or conflict of interests.

CONSENT

Written consent not obtained by the patient, as all imaging and pathology described was obtained retrospectively and de-identified.

QUESTIONS

Question 1:

Which of the following is the most common prostate cancer type type and most accurate corresponding percentage?

1. adenocarcinoma, 65%
2. squamous cell carcinoma, 72%
3. neuroendocrine prostate cancer, 41%
4. adenocarcinoma, 99% (applies)
5. signet ring cell carcinoma, 87%

Explanation question 1:

1. The acinar adenocarcinoma subtype is the most common type, however it comprises approximately 99% of prostate malignancy, not 65%. [Prostate cancer is the most common extra-cutaneous malignancy in males [1]. More than ninety percent of prostate malignancy are of the acinar adenocarcinoma subtype, which are androgen-driven tumors and often treated with androgen deprivation therapy]

2. Adenosquamous carcinoma subtype of prostate cancer has been reported, however it is much less prevalent than adenocarcinoma. [Prostate cancer is the most common extra-cutaneous malignancy in males [1]. More than ninety percent of prostate malignancy are of the acinar adenocarcinoma subtype, which are androgen-driven tumors and often treated with androgen deprivation therapy]

3. Neuroendocrine prostate cancer is a rare subtype. [However, multiple uncommon histologic variants exist [3], including neuroendocrine prostate cancer (NEPC), which makes up 0.5-2% [5-7] of prostate cancer cases.]

4. The acinar adenocarcinoma subtype is the most common type, comprising approximately 99% of prostate malignancy. [Prostate cancer is the most common extra-cutaneous malignancy in males [1]. More than ninety percent of prostate malignancy are of the acinar adenocarcinoma subtype, which are androgen-driven tumors and often treated with androgen deprivation therapy]

5. Signet ring cell carcinoma subtype of prostate cancer has been reported, however is much less prevalent than adenocarcinoma. [Prostate cancer is the most common extra-cutaneous malignancy in males [1]. More than ninety percent of prostate malignancy are of the acinar adenocarcinoma subtype, which are androgen-driven tumors and often treated with androgen deprivation therapy]

Question 2:

Which of the following is/are correct regarding neuroendocrine prostate cancer (select all that apply)?

1. It is a common malignancy.
2. It most often arises spontaneously.
3. The median survival is approximately one year. (applies)
4. It is typically diagnosed early.
5. It most often arises in the setting of androgen deprivation therapy for prostate adenocarcinoma. (applies)

Explanation question 2:

1. Neuroendocrine prostate cancer is a rare subtype. [However, multiple uncommon histologic variants exist [3], including neuroendocrine prostate cancer (NEPC), which makes up 0.5-2% [5-7] of prostate cancer cases]

2. Neuroendocrine prostate cancer rarely arises spontaneously, and more often arises as a mechanism of treatment resistance in the setting of therapy for prostate adenocarcinoma. [NEPC can rarely originate from de novo mutations [5], but it more commonly arises in the course of evolving treatment resistance to androgen deprivation therapy]

3. Neuroendocrine prostate cancer is aggressive with median survival of approximately 12 months. [NEPC is the most lethal prostate malignancy subtype, with median survival of 9.8-13.1 months]

4. Neuroendocrine prostate cancer is often diagnosed with metastases. [NEPC is the most lethal prostate malignancy subtype, with median survival of 9.8-13.1 months [8-9], 5-year overall survival of 12.6% [10], and distant metastases present at time of diagnosis in approximately half of patients]

5. Neuroendocrine prostate cancer rarely arises spontaneously, and more often arises as a mechanism of treatment resistance in the setting of therapy for prostate adenocarcinoma. [NEPC can rarely originate from de novo mutations [5], but it more commonly arises in the course of evolving treatment resistance to androgen deprivation therapy]

Question 3:

Which of the following is correct regarding the relationship between neuroendocrine tumors and prostate biomarkers?

1. Progression of neuroendocrine prostate cancer correlates with rising prostate specific antigen levels.
2. Androgen signaling is preserved in neuroendocrine prostate cancer, however alterations in systemic estrogen levels affect the levels of prostate specific antigen.
3. Nuclear medicine imaging techniques such as PET scan using prostate specific membrane antigen is a valuable tool in detecting and monitoring neuroendocrine prostate cancer.
4. Prostate specific antigen is not useful because androgen deprivation therapy administered for prostate adenocarcinoma falsely depresses measurable levels of prostate biomarkers.
5. The normal androgen signaling pathway is disrupted in neuroendocrine prostate cancer, which can produce false reassurance for clinical monitoring with prostate specific antigen levels. (applies)

Explanation question 3:

1. Neuroendocrine prostate cancer has disruption of the androgen signaling pathway which also interrupts the correlation with prostate specific antigen levels. [As such, the typical androgen receptor signaling pathway is lost or dysregulated, and the classical correlation with prostate specific antigen (PSA) levels is often absent during progression of NEPC]

2. Neuroendocrine prostate cancer has disruption of the androgen signaling pathway which also interrupts the correlation with prostate specific antigen levels. [As such, the typical androgen receptor signaling pathway is lost or dysregulated, and the classical correlation with prostate specific antigen (PSA) levels is often absent during progression of NEPC]

3. Neuroendocrine prostate cancer may provide false negative results with conventional "prostate-specific" imaging techniques because of the loss of the normal androgen signaling physiologic pathway. [Because NEPC often arises in the setting of CRPC with loss of the typical prostate biochemical signaling pathways, certain "prostate specific" imaging techniques such as PET with PSMA may provide false negatives in these cases.]

4. Disruption of the androgen signaling pathway, rather than iatrogenic androgen deprivation therapy, is responsible for the dissociation between disease status and prostate specific antigen neuroendocrine prostate cancer. [As such, the typical androgen receptor signaling pathway is lost or dysregulated, and the classical correlation with prostate specific antigen (PSA) levels is often absent during progression of NEPC]

5. Neuroendocrine prostate cancer has disruption of the androgen signaling pathway which also interrupts the correlation with prostate specific antigen levels. [As such, the typical androgen receptor signaling pathway is lost or dysregulated, and the classical correlation with prostate specific antigen (PSA) levels is often absent during progression of NEPC]

Question 4:

Which of the following imaging findings is most suspicious for neuroendocrine prostate cancer in the setting of a patient with known prostate adenocarcinoma on treatment?

1. Bilateral hydronephrosis from bulky pelvic lymphadenopathy.

2. New lytic bone lesions with aggressive characteristics. (applies)

3. Stable sclerotic lesions throughout the axial skeleton.

4. Heterogeneous pelvic mass centered at the prostate.

5. Irregular nodularity of the posterior bladder wall.

Explanation question 4:

1. Pelvic lymphadenopathy is a common manifestation of prostate adenocarcinoma, and statistically is most likely related to this most common prostate malignancy subtype. [In patients with known prostate adenocarcinoma, findings of metastatic disease are often presumed to represent progression of the original malignancy type. Supportive findings include increasing PSA levels and typical prostate adenocarcinoma metastatic pattern, including pelvic lymphadenopathy which sometimes presents as obstructive uropathy, potentially direct invasion of the bladder or rectal wall, and diffuse sclerotic osseous lesions]

2. Lytic bone lesions are atypical for prostate malignancy. Particularly when new and progressing, if the patient does not have other signs of adenocarcinoma progression such as rising prostate specific antigen levels, this finding should raise the suspicion for neuroendocrine prostate cancer, and biopsy should be considered. [Suspicious findings include aggressive metastatic progression with atypical features, such as lytic bone lesions and low PSA levels, and confirmation with tissue sampling is required to confirm the diagnosis]

3. Sclerotic bone lesions are a common manifestation of prostate adenocarcinoma, and statistically is most likely related to this most common prostate malignancy subtype. [In patients with known prostate adenocarcinoma, findings of metastatic disease are often presumed to represent progression of the original malignancy type. Supportive findings include increasing PSA levels and typical prostate adenocarcinoma metastatic pattern, including pelvic lymphadenopathy which sometimes presents as obstructive uropathy, potentially direct invasion of the bladder or rectal wall, and diffuse sclerotic osseous lesions]

4. A mass arising from the prostate is a common manifestation of prostate adenocarcinoma, and statistically is most likely related to this most common prostate malignancy subtype. [In patients with known prostate adenocarcinoma, findings of metastatic disease are often presumed to represent progression of the original malignancy type. Supportive findings include increasing PSA levels and typical prostate adenocarcinoma metastatic pattern, including pelvic lymphadenopathy which sometimes presents as obstructive uropathy, potentially direct invasion of the bladder or rectal wall, and diffuse sclerotic osseous lesions]

5. Direct invasion of the posterior bladder wall is a common manifestation of prostate adenocarcinoma, and statistically is most likely related to this most common prostate malignancy subtype. [In patients with known prostate adenocarcinoma, findings of metastatic disease are often presumed to represent progression of the original malignancy type. Supportive findings include increasing PSA levels and typical prostate adenocarcinoma metastatic pattern, including pelvic lymphadenopathy which sometimes presents as obstructive uropathy, potentially direct invasion of the bladder or rectal wall, and diffuse sclerotic osseous lesions]

Question 5:

Which of the following is false regarding treatment and outcomes of neuroendocrine prostate cancer?

1. Neuroendocrine prostate cancer is treated the same way as prostate adenocarcinoma. (applies)

2. Neuroendocrine prostate cancer is typically treated similarly to small cell lung cancer.

3. The majority of patients with neuroendocrine prostate cancer do not respond to currently available treatment regiments.

4. Studies are ongoing regarding novel biomarkers for future treatment of neuroendocrine prostate cancer.

5. Even with treatment, less than half of patients survive five years after diagnosis with neuroendocrine prostate cancer.

Explanation question 5:

1. Neuroendocrine prostate cancer is typically treated with platinum-based therapies, not androgen deprivation therapy,

because neuroendocrine prostate cancer most commonly arises as a mechanism of resistance to the latter treatment. [Treatment for NEPC currently employs chemotherapy regimens that have been studied for small cell lung cancer, which has similar neuroendocrine cell phenotype, typically with platinum-based therapies]

2. Neuroendocrine prostate cancer is usually treated with platinum-based chemotherapy, like small cell lung cancer, because of the similarities in neuroendocrine phenotype. [Treatment for NEPC currently employs chemotherapy regimens that have been studied for small cell lung cancer, which has similar neuroendocrine cell phenotype, typically with platinum-based therapies]

3. Neuroendocrine prostate cancer response rate is less than 50%. [However, survival remains poor, with less than 50% response rate in typical platinum-based combination chemotherapy and less than 20% overall five-year survival]

4. Immune checkpoint inhibitors and novel biomarker targets are under investigation for future neuroendocrine prostate cancer treatments. [Combination with immune checkpoint inhibitors and novel biomarker targets are under investigation]

5. Neuroendocrine prostate cancer 5-year survival is less than 20%. [However, survival remains poor, with less than 50% response rate in typical platinum-based combination chemotherapy and less than 20% overall five-year survival]

REFERENCES

1. Salinas CA, Tsodikov A, Ishak-Howard M, Cooney KA. Prostate cancer in young men: an important clinical entity. *Nat Rev Urol*. 2014; 11(6): 317-323. PMID: 24818853.
2. Grignon DJ. Unusual subtypes of prostate cancer. *Mod Pathol*. 2004; 17(3): 316-327. PMID: 14976541.
3. Li J, Wang Z. The pathology of unusual subtypes of prostate cancer. *Chin J Cancer Res*. 2016; 28(1): 130-143. PMID: 27041935.
4. Conteduca V, Oromendia C, Eng KW, et al. Clinical features of neuroendocrine prostate cancer. *Eur J Cancer*. 2019 Nov; 121:7-18. PMID: 31525487.
5. Taher A, Jensen CT, Yedururi S, et al. Imaging of neuroendocrine prostatic carcinoma. *Cancers (Basel).* 2021; 13(22): 5765. PMID: 34830919.
6. Ather MH, Siddiqui T. The genetics of neuroendocrine prostate cancers: a review of current and emerging candidates. *Appl Clin Genet*. 2012; 8:105-10. PMID: 23776386.
7. Chen J, Shi M, Chuen Choi SY, et al. Genomic alterations in neuroendocrine prostate cancer: A systematic review and meta-analysis. *BJUI compass*. 2023; 4(3): 256-265. PMID: 37025467.
8. Abbas F, Civantos F, Benedetto P, Soloway MS. Small cell carcinoma of the bladder and prostate. *Urology*. 1995; 46(5): 617-630. PMID: 26261754.
9. Spiess PE, Pettaway CA, Vakar-Lopez F, et al. Treatment outcomes of small cell carcinoma of the prostate: a single-center study. *Cancer*. 2007; 110(8): 1729-1737. PMID: 17786954.
10. Parimi V, Goyal R, Poropatich K, Yang XJ. Neuroendocrine differentiation of prostate cancer: a review. *Am J Clin Exp Urol*. 2014; 2(4): 273-285. PMID: 25606573.
11. Dos Santos G, Fontes MG, Engler H, Alonso O. Intraindividual comparison of 68Ga-DOTATATE PET/CT vs. 11C-choline PET/CT in patients with prostate cancer in biochemical relapse: In vivo evaluation of the expression of somatostatin receptors. Rev *Esp Med Nucl Imagen Mol (Engl Ed).* 2019; 38(1): 29-37. PMID: 30442558.
12. Alabi BR, Liu S, Stoyanova T. Current and emerging therapies for neuroendocrine prostate cancer. *Pharmacol Ther*. 2022: 108255. PMID: 35905791.
13. Beltran H, Demichelis F. Therapy considerations in neuroendocrine prostate cancer: what next? *Endocr Relat Cancer*. 2021; 28(8): T67-T78. PMID: 34111024.
14. Bhagirath D, Liston M, Akoto T, et al. Novel, non-invasive markers for detecting therapy induced neuroendocrine differentiation in castration-resistant prostate cancer patients. *Sci Rep*. 2021; 11(1): 8279. PMID: 33859239.
15. Sasagawa H, Numakura K, Mori M, et al. Androgen deprivation therapy caused a drastic proliferation of B-cell lymphoma with IgG4-related disease in patients with prostate cancer: a case report. *J Cancer Res Clin Oncol*. 2023; 149(16): 15091-15094. PMID: 37688628.

FIGURES

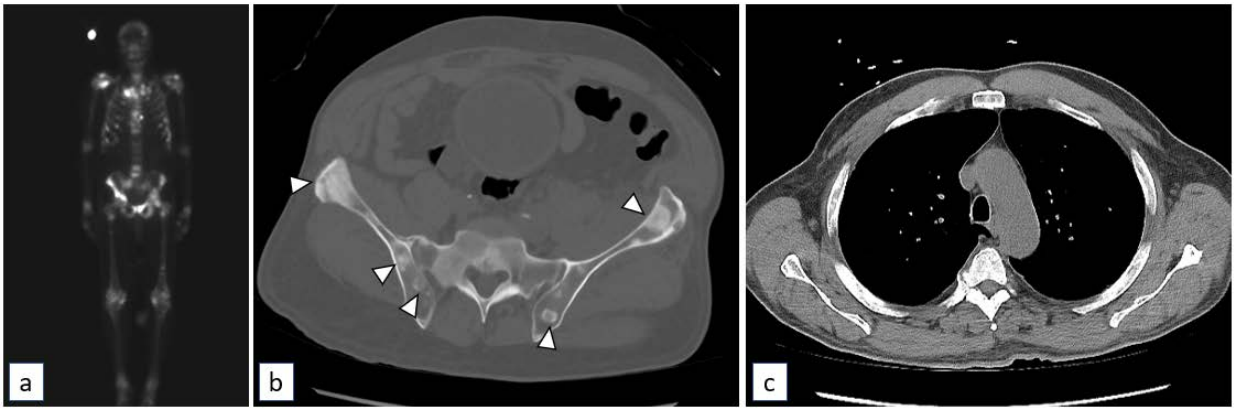

Figure 1: Initial staging imaging at the time of prostate adenocarcinoma diagnosis. **a.** Nuclear medicine bone scan with extensive axial and appendicular skeletal foci of increased uptake, compatible osseous metastases, including the pelvis, sternum, right clavicle, multiple ribs and vertebral bodies. **b.** Axial CT through the pelvis showing numerous sclerotic metastatic lesions (arrowheads), typical for prostate adenocarcinoma. **c**. Axial CT through the chest with unremarkable initial appearance of the chest wall.

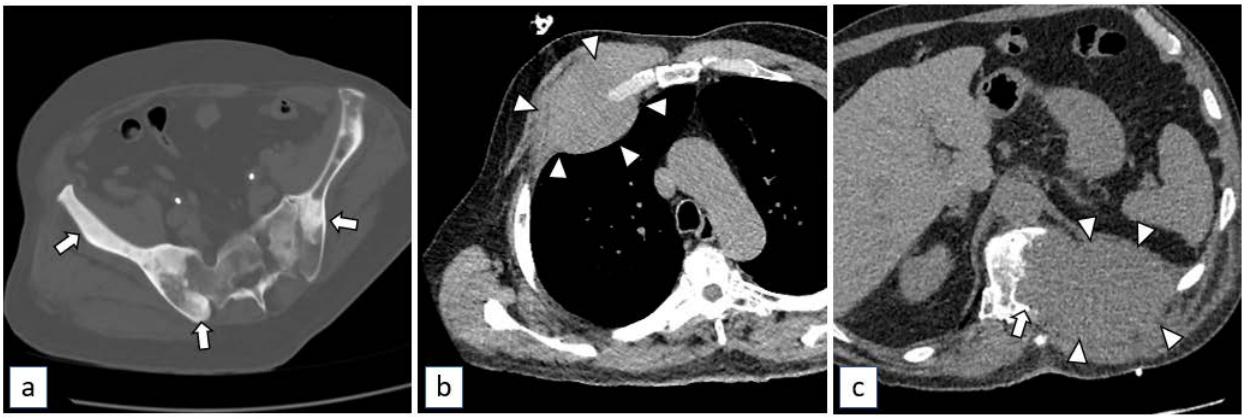

Figure 2: Six-month follow up imaging at the time of second biopsy showing NEPC. **a.** Axial CT through the pelvis showing progression and more confluent regions of the numerous sclerotic metastatic lesions (arrows) since the prior study. **b.** Axial CT through the chest with a new metastatic lesion centered at the anterior right third rib, with destructive lytic appearance and large soft tissue component extending to intrathoracic and extrathoracic spaces (arrowheads), including the subpectoral tissues **c**. More inferiorly, an additional new destructive lesion (arrowheads) through the posterior left twelfth rib, also invading the thoracic spine and reaching the canal (arrow) at that level.

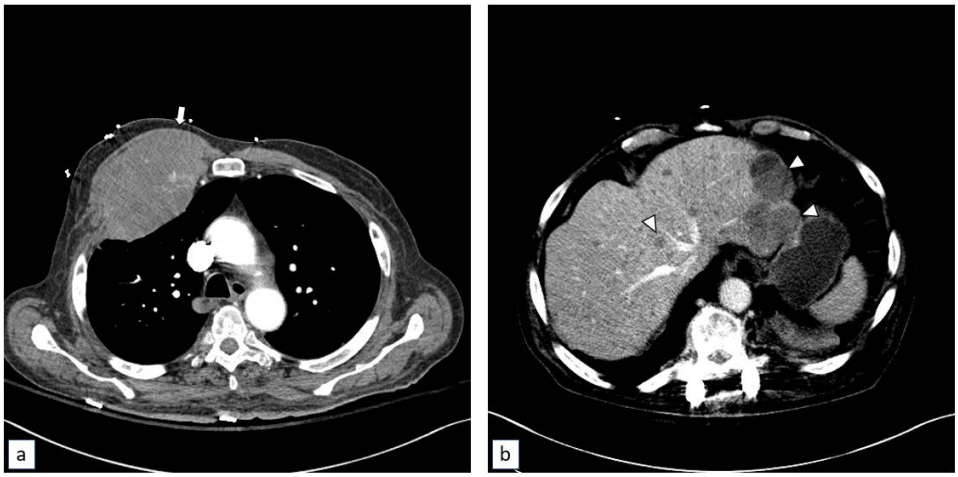

Figure 3: One month later, progression of metastatic disease is noted on imaging for other clinical indications. **a.** Axial CTA through the chest with interval enlargement of the right chest wall lesion (arrow), measuring approximately 40% larger, with heterogeneous early internal enhancement evident on this contrast enhanced study. **b.** Axial CT through the abdomen shows numerous new hepatic hypodensities consistent with metastatic spread, largest in the left hepatic lobe (arrowheads).

KEYWORDS

Neuroendocrine prostate cancer; prostate cancer; castration-resistant prostate cancer; treatment resistance; androgen deprivation

ABBREVIATIONS

NEPC = NEUROENDOCRINE PROSTATE CANCER
CRPC = CASTRATION-RESISTANT PROSTATE CANCER
PSA = PROSTATE SPECIFIC ANTIGEN
PSMA = PROSTATE SPECIFIC MEMBRANE ANTIGEN

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