


A potential prognostic marker in primitive lung neuroendocrine tumor: A case report

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Abstract

Background: The diagnosis and monitoring of primitive lung neuroendocrine tumors (lung pNETs) are usually performed by the measurement of serum chromogranin A (CgA) and urinary 5-hydroxyindolacetic acid (5-HIAA) levels. However, imaging techniques are necessary due to the poor diagnostic efficiency of the laboratory tests.

Methods: A total-body computed tomography and bone scintigraphy scans showed multiple hepatic and bone metastases of a 55-year-old man affected by well-differentiated lung pNETs without severe initial symptoms. After diagnosis, he started therapy and was monitored with serum, urinary markers, and imaging techniques.

Results: During follow-up, the urinary 5-HIAA levels did not significantly increase, while serum CgA and urinary parahydroxyphenylacetic acid (pHPAA) levels (urinary organic acid physiologically present in the urines of healthy subjects) showed significant increases related to worsening clinical condition.

Conclusions: The early increase in urinary pHPAA levels—usually not dosed in pNET patient monitoring—could be a promising prognostic marker.

Keywords

Lung pNETs, pHPAA, CgA, 5-HIAA

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Introduction

Neuroendocrine tumors (NETs) are rare tumors that originate from the cells of the diffuse neuroendocrine system. The most frequent primary sites are the gastrointestinal (60%–70%) and the tracheo-bronchopulmonary (20%–30%) tract¹; other regions are skin, thyroid, parathyroid, and adrenal glands (10%) for example. Lung neuroendocrine tumors can be classified into neuroendocrine cell hyperplasia and tumorlets, neuroendocrine morphology tumors, non-microcytomas with neuroendocrine differentiation, and other lung tumors with neuroendocrine features. Many patients affected with primitive lung neuroendocrine tumors (lung pNETs) are asymptomatic at the time of diagnosis or have non-specific symptoms of respiratory distress such as asthma or chronic obstructive pulmonary disease, that often delay the diagnosis.²

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Although more than 90% of lung pNETs are non-functional, patients with a functional (secretory) component present hormonal symptoms (wheezing, skin redness, and diarrhea) due to the secretion of hormones and peptides.³ Diagnostic procedures include imaging tests, such as total-body computed tomography (CT), ultrasounds, bone scintigraphy, positron emission tomography/CT (PET/CT), magnetic resonance imaging, and angiography, in order to evaluate disease location and extent.⁴ In addition, the diagnosis and follow-up of NETs require serum chromogranin A (CgA) and 24-hour urinary 5-hydroxyindolacetic acid (5-HIAA) to be performed. Serum neuron-specific enolase (NSE)—even though it is not recommended in the management of patients with NETs—has been demonstrated to be elevated in 30%–50% of subjects with NETs. Preliminary data have reported urinary para-hydroxyphenylacetic acid (pHPAA, a tyrosine metabolite physiologically excreted in the urine of healthy people) as a useful marker, together with 5-HIAA, for the management of NETs patients.⁵

Case description

A 55-year-old man with no relevant medical history, presented to our facility in January 2018 with cough and wheezing. A thorax CT scan showed a 19 mm maximum diameter solid nodule with irregular margins into the left upper lobe connected to an ipsilateral superior hilar lymph node agglomeration of 45 mm (maximum diameter). The total-body CT scan (Figure 1(a), right panel) revealed the presence of multiple liver and bone metastases, which were confirmed by bone scintigraphy. A liver biopsy performed in March 2018 showed a well-differentiated neuroendocrine tumor. After a multidisciplinary evaluation, ⁶⁸Ga-labelled DOTA-Tyr octreotide (⁶⁸Ga-DOTATOC) PET/CT was performed to confirm somatostatin receptor expression and disease staging. ⁶⁸Ga-DOTATOC PET/CT functional imaging revealed an abnormal significant uptake of the tracer in the left upper lobe of the lung (SUV_{max} 13.6), in the ipsilateral hilar region (SUV_{max} 30.3), and in multiple liver (SUV_{max} 40.0) and bone lesions (SUV_{max} 48.7) (Figure 1(a), left panel). In April 2018, the patient started therapy with octreotide long-acting release (LAR) 30 mg intramuscularly every 28 days. No adverse events were reported during the treatment in accordance with Common Terminology Criteria for Adverse Events (CTCAE criteria version 4.0).

The patient was monitored by periodic total-body CT scans, which showed a stable disease (Figure 1(b): total-body CT scan performed in November 2018). After November 2018, disease progression (Figure 1(c), left panel) occurred with a resumption of symptoms. Thereafter, the patient was included in a clinical, multi-center, double-blinded, randomized trial of axitinib versus

placebo and was monitored every 12 weeks by means of total-body CT scans in accordance with Response Evaluation Criteria in Solid Tumors (RECIST criteria version 1.1) and laboratory tests. The 24-hour urinary levels of 5-HIAA and pHPAA were monitored from March 2019 until March 2020 by means of high-pressure liquid chromatography (HPLC) with electrochemical detection in 24-hour urine samples. Serum CgA levels were determined on KRYPTOR compact PLUS instrumentation and contextually serum NSE (as a marker of neuroendocrine differentiation) levels on the Roche COBAS 6000 platform. The octreotide LAR treatment allowed the achievement of stable disease until January 2020, when multiple lesions in the brain were documented (Figure 1(c), right panel). To date, the patient is continuing to perform encephalic radiotherapy, which is planned to reach a total dose of 30 Gy.

Conclusion

From March 2019 to March 2020, the patient was monitored by determining serum CgA and urinary 5-HIAA every 12 weeks. Urinary 5-HIAA chromatograms obtained with the HPLC method enabled the detection and measurement of pHPAA levels simultaneously (Figure 2). As shown in Figure 3 and Table 1, only serum CgA presented high levels at baseline with an important increasing trend from the first to the last follow-up. Urinary 5-HIAA levels augmented slightly by 12 and 48 weeks, while serum NSE presented a mild increase throughout the monitoring, respectively (Table 1). Unexpectedly, the urinary pHPAA levels (within the reference range at baseline) showed a great increase, which appeared earlier (at 12–24 weeks) when compared to the urinary 5-HIAA level's trend (Figure 2, Table 1). Urinary pHPAA is an important metabolite of tyrosine⁶ and is related to the disturbance of tyrosine metabolism and liver disease. Tyrosine is an amino acid that originates from the hydroxylation of phenylalanine,⁷ precursor of various substances such as catecholamines, presenting a relationship with some types of cancer.^{8–10} In particular, some studies report variations of pHPAA in hepatocellular carcinoma and breast cancer.^{9–10} The guidelines for the diagnosis and follow-up of NETs indicate serum CgA, urinary 5-HIAA, and serum NSE determinations as the gold standard. Previous retrospective preliminary data have reported increased levels of urinary pHPAA in NET patients.⁵

In this case report, urinary pHPAA was evaluated during patient monitoring and was found to have increased earlier than the urinary 5-HIAA levels with an increasing trend during follow-up. This finding suggests the possibility of combining urinary pHPAA determination with serum CgA in the management of NET patients, in particular during follow-up. Moreover, HPLC elution of urinary pHPAA

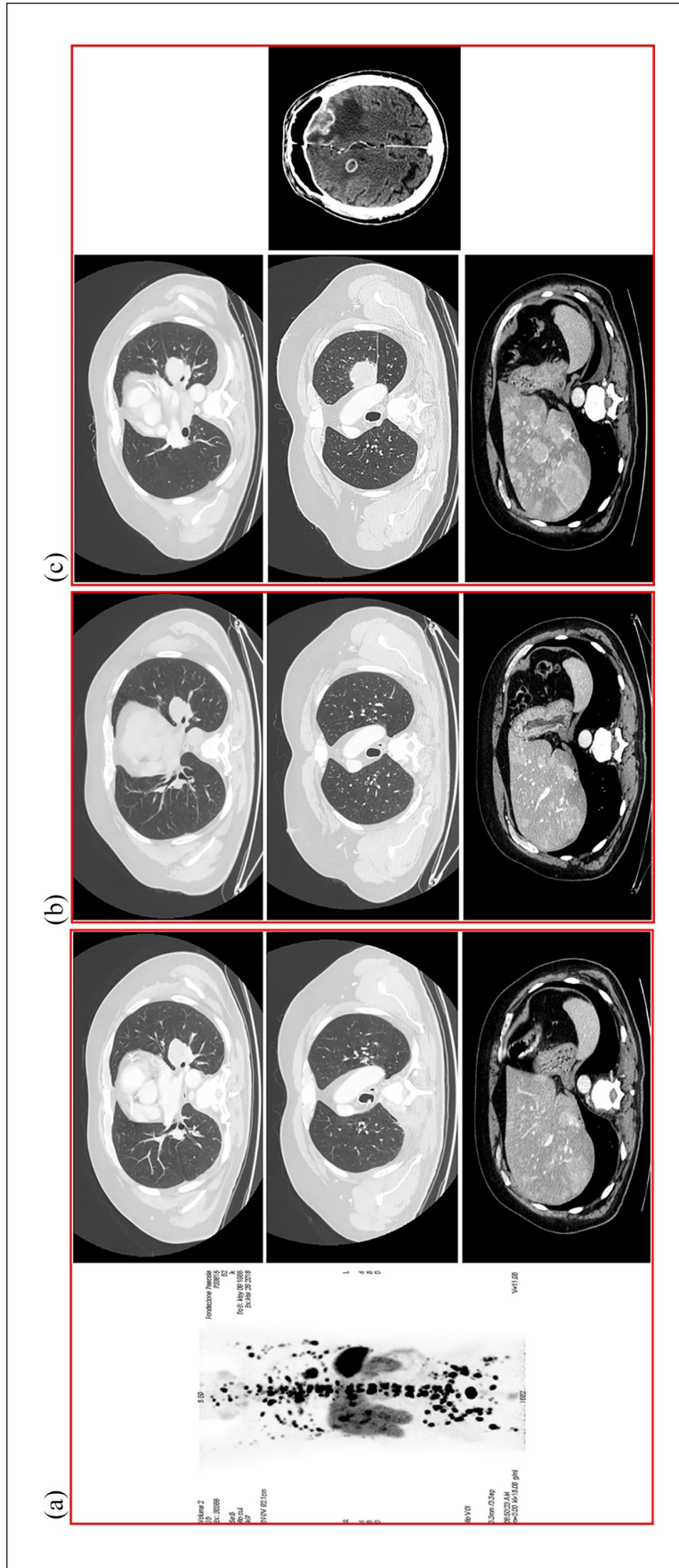


Figure 1. (a) (left panel): PET/CT using ⁶⁸Ga-labelled DOTA-Tyr octreotide shows multiple areas of abnormal uptake into lungs, lymph nodes, liver, and bone; (right panel): total-body CT scan shows a pulmonary left hilar lesion and multiple liver lesions. (b) A total-body CT scan during octreotide long-acting release therapy shows stable disease. (c) A total-body PET/CT scan shows progressive disease at the liver (left panel, November 2018) and the brain (right panel, January 2020) during the last follow-up. PET/CT: positron emission tomography/computed tomography.

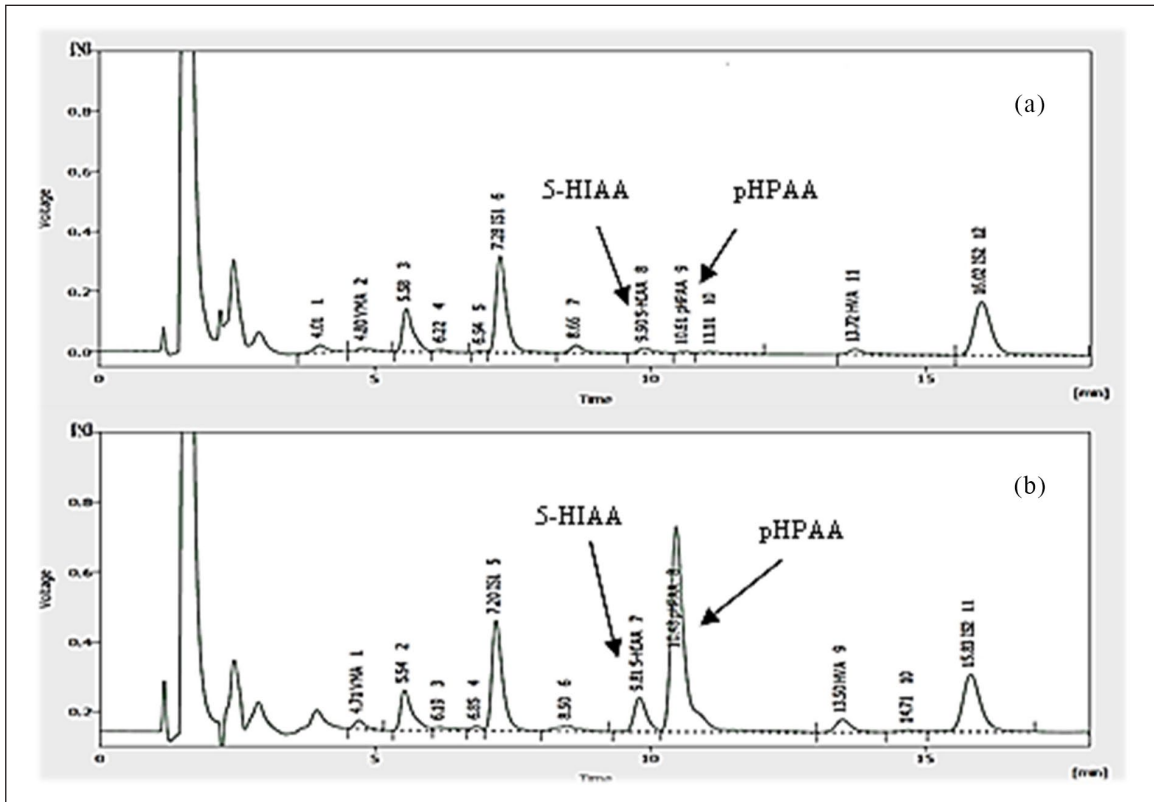


Figure 2. HPLC chromatograms. (a) Urinary 5-HIAA and pHPAA normal levels at first follow-up. (b) Urinary 5-HIAA and pHPAA higher levels at last follow-up.
 HPLC: high-pressure liquid chromatography.

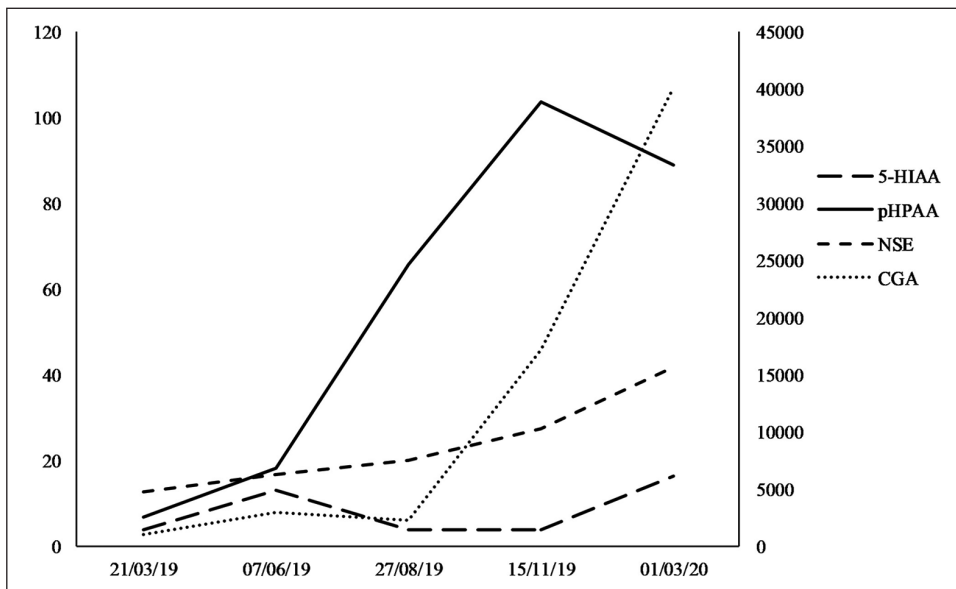


Figure 3. Biomarker monitoring: the scale on the left refers to serum NSE (ng/mL), urinary 5-HIAA (mg/24h), and urinary pHPAA (µmol/mmol creatinine); the scale on the right refers to serum CgA (ng/mL).

in the same chromatogram used for urinary 5-HIAA determination makes it technically feasible and simple to detect.

In conclusion, the described case focuses on the possible utility of taking into account urinary pHPAA levels,

Table 1. Monitoring of serum and urinary markers during the clinical trial of axitinib versus placebo.

	Baseline	12 weeks	24 weeks	36 weeks	48 weeks
Urinary 5-HIAA (mg/24h) reference range: 0.7–8.2	3.7	12.9	4.0	3.8	16.5
Urinary pHPAA ($\mu\text{mol}/\text{mmol}$ creatinine) reference range: ≤ 9.7	6.6	18.3	65.6	103.7	88.8
Serum NSE (ng/mL) reference range: 0.0–17.0	12.6	16.7	20.0	27.3	41.8
Serum CgA (ng/mL) reference range: 6.2–84.7	953.0	3000.0	2257.0	17180.0	40120.0

integrating NET laboratory diagnosis with its detection on HPLC chromatograms. Nevertheless, this potential approach should be investigated in larger series of patients.

Author contributions

Luigi Russo and Bruna Grilli contributed equally to this work.


Declaration of Conflicting Interests

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References

1. Wolin EM. Advances in the diagnosis and management of well-differentiated and intermediate-differentiated neuroendocrine tumors of the lung. *Chest* 2017; 151: 1141–1146.
2. Hendifar AE, Marchevsky AM and Tuli R. Neuroendocrine tumors of the lung: current challenges and advances in the diagnosis and management of well-differentiated disease. *J Thorac Oncol* 2017; 12: 425–436.
3. Melosky B. Low grade neuroendocrine tumors of the lung. *Front Oncol* 2017; 7: 119.
4. Hofland J, Feelders RA, Brabander T, et al. Recent developments in the diagnosis and therapy of well-differentiated neuroendocrine tumours. *Neth J Med* 2018; 76: 100–108.
5. Grilli B, Russo L, Barchiesi V, et al. Implementation of a HPLC method for the evaluation of urinary 4-hydroxyphenylacetic acid in patients with neuroendocrine tumors. *Biochim Clin* 2018; 42SS1: S154.
6. Geck RC and Toker A. Nonessential amino acid metabolism in breast cancer. *Adv Biol Regul* 2016; 62: 11–17.
7. Wiggins T, Kumar S, Markar SR, et al. Tyrosine, phenylalanine, and tryptophan in gastroesophageal malignancy: A systematic review. *Cancer Epidemiol Biomarkers Prev* 2015; 24: 32–38.
8. Suzuki Y, Tokinaga-Uchiyama A, Mizushima T, et al. Normalization of abnormal plasma amino acid profile-based indexes in patients with gynecological malignant tumors after curative treatment. *BMC Cancer* 2018; 18: 973.
9. Feng L, He YQ, Xu GH, et al. Determination of tyrosine and its metabolites in human serum with application to cancer diagnosis. *Anal Lett* 2014; 47: 1275–1289.
10. Yang YI, Liu F and Wan YQ. Simultaneous determination of 4-hydroxyphenyl lactic acid, 4-hydroxyphenyl acetic acid, and 3,4-hydroxyphenyl propionic acid in human urine by ultra-high-performance liquid chromatography with fluorescence detection. *J Sep Sci* 2017; 40: 2117–2122.