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CASE REPORT

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A New Perspective in Diagnosis of Neuroendocrine Tumors and Pseudo Pheochromocytomas, Understanding the Biology Behind a Mislabeled Medical Terminology

M Nezami MD[1], Jason Samarasena MD[2], Reza Nazemi[3], Mark Kidd PhD[4] and Steven Hager MD[5]

[1]Sahel Oncology LLC, Orange Coast Medical Center of Hope, Cancer Research and Life Foundation

[2]University of California-Irvine (UCI)

[3]Cedar Sinai Hospital, Endocrine Department

[4]WREN Laboratory Molecular Diagnostics

[5]California Cancer Associates for Research and Excellence (C Care)

[6] Yale University School of Medicine

ABSTRACT

Recently the incidence of undiagnosed hypertension that does not fit into either category of essential hypertension or secondary hypertension is becoming largely increased. Most of these cases are attributed to anxiety or forms of panic attacks associated with high blood pressure. Some in fact are lethal yet clinicians have been challenged to know the real cause of the disease. The term pseudopheochromocytoma widely used for patients who have typical presentation of pheochromocytoma but yet no concrete evidence of disease manifested in their imaging or lab reports to suggest increased production of adrenaline or neurepinephrine, as seen in typical pheochromocytomas. These patients suffer from life threatening attacks of hypertension, yet the only medical revenue offered are anxiolytics, or tricyclic antidepressants. Here we review a case of suspected pheochromocytoma and we present a novel theory about the real player behind all cases of pseudopheochromocytomas. Since in contrast to all other tumors, performing a tissue biopsy is detrimental in the case of pheochromocytomas, and therefore no one logically considers a tissue biopsy for adrenal gland, liquid biopsy(NETest by WREN Laboratory) is a great substitute with high accuracy to replace the tissue biopsy. We conclude that performing liquid biopsy on all cases of pseudopheochromocytoma is essentially life saving and can lead the clinician to appropriate course of action, when the other labs and functional imaging are inconclusive or negative. This is the very perfect example of why the traditional thinking of required presence of metanephrines in urine or blood, and nuclear studies(Dotetate scan/ Octrascan/ MiBG scan, etc…) for diagnosis of pheochromocytoma and surgical interventions depending on such tests is outdated.

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Background

For centuries clinicians have been fooled by mis characterizing the patients, with hypertension and psychoemotional disease as Pseudopheochromocytomas (which are clinically same as pheochromocytomas) with borderline or normal labs and unfunctional presence of adenomas in imaging. Most of these patients suffered from adrenal so called " incidentalomas" or benign cortical adenomas when investigated. This is when some prior literature has suggested that in Pseudo pheochromocytomas there is also excessive epinephrine secretion in response to psychological stimuli, specially the ones that carry the PTSD type of response in individuals who has sustained trauma from repressive these emotions we present an interesting case report of a patient with clinical manifestation of pheochromocytoma and drastic response to alpha blockers, who responds to surgical intervention , by means of an adrenalectomy; yet pathology fails to reveal what is diagnostic for pheochromocytoma. The literature search revealed one similar case, with similar presentation, however in our cases even the metanephrines were negative, and the only positive test was liquid biopsy (NETest by WREN Laboratory) that revealed the true cause of his disease as neuroendocrine tumor [1].

Case History

53 years old male with history of HTN and DM, for about 2 years, and family history of colon cancer in mother, taking infrequent propranolol, as only medication.

Contact: M Nezami MD, Sahel Oncology LLC, Orange Coast Medical Center of Hope, Cancer Research and Life Foundation.

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Acute onset of malignant paroxysmal HTN, status post receiving ten sessions of Calcium disodium EDTA, referred to ER for blood pressure of 240/130, pulse of 120 associated with palpitation, headache. Based on prior medical history patient was sent home to follow with his PMD(12/18/23).

Lab indicated no metabolic finding except Glc of 180, and A1C of 7.2.

Patient remained unstable with elevated blood pressure same day and day after, received amlodipine, Lisinopril and hydralazine to lower the blood pressure. (self treated).

Further follow up with cardiologist did not prove to be fruitful, or diagnostic. His ECG was normal, and an echo was performed which was in normal range with EF of 60 percent.

He continued to suffer from episodic malignant pressure that lasted 20 minutes each time, and recurred almost daily. He further referred to his old records where he found an incidentaloma(adrenal nodule of 1.5 cm, that was seen in his prior CT of abdomen/ pelvis, in November 2023, during a work up performed for a flank pain, to rule out kidney stone.

With high suspicion of Pheochromocytoma, he referred to an endocrinologist at UCLA, who ordered an adrenal nuclear scan(DOTETATE) performed on 2/2/24-which was read as negative, although several skeletal masses were seen, and upon further evaluation with MRI, was shown be hemangiomas.

He further was evaluated with plasma and 24 hour urine catecholamines and 5 HIAA, which showed increased 5 HIAA of 12.7 (normal less than 6) and increased epinephrine of 92 (normal less than 60). All other abs including serum metanephrines came back normal.

He further started Prazosin at 0.5 mg twice a day, which immediately reduced the blood pressure to acceptable range and he was able to minimize or stop all other meds. During this time, he also started to have significant GI issues, including loss of appetite and loose stool. His tachycardic episodes mostly was prompted by eating a histamine releasing food, such as spices or sea food. As a result of daily hypertensive attacks, he lost over 35 lbs, and repeat labs showed Hb A1C at 5.6.

Further imaging with abdominal MRI with contrast and MIBG scan were all negative, except the stable size 1.5 cm left adrenal lesion which continued to be non avid in MIBG as well as FDG PET scan. He saw several surgeons to possibly remove the adrenal mass with adrenalectomy but they both refused to operate on him as the diagnosis of Pheochromocytoma was not made, due to negative metanephrines and chromogranin– A.

His labs also ruled out mastocytosis, and insulinoma, gastrinoma and other possible neuroendocrine tumors. However his NETest liquid biopsy through WREN Lab. was positive, showing a score of 73 (high risk). (image 1)

He continued Prazosin for 3 months, with partial response to the medication, still experiencing hypertensive attacks at a much less frequency, until in May of 2024, when he was referred for diagnostic left adrenalectomy at Cedar Sinai hospital, to evaluate a possible functional adrenal adenoma (producing epinephrine), or small pheochromocytoma. His pathology was negative for pheochromocytoma but positive for scattered synaptophysin staining, typical for pheochromocytoma.

Clinically he was able to switch Prazosin to Carvediol which was further tapered and completely stopped, and remained normotensive after surgery. His blood pressure ranged from 109/76 to 129/80, and his NETest responded with reduction of score from 73 to 26. (see image 2)

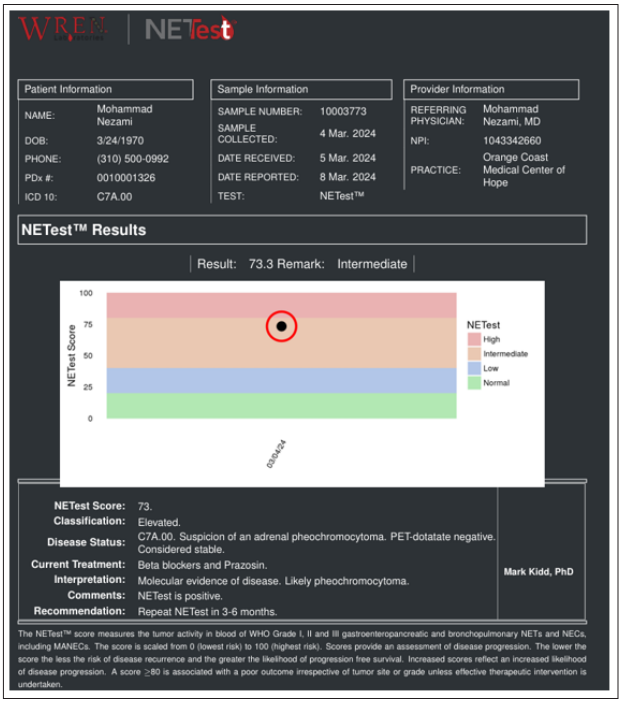

Image 1: NE Test Liquid Biopsy

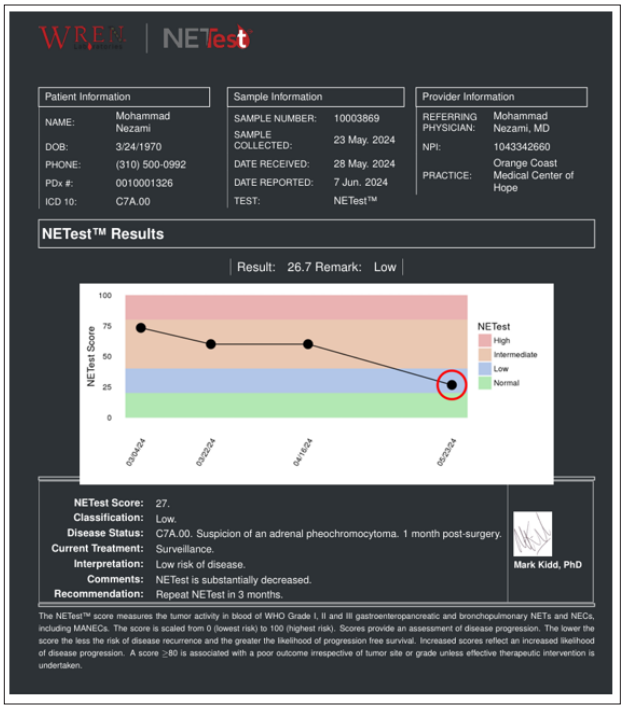

Image 2: Post Surgical Liquid Biopsy

Discussion

By the review of literature it has come to our notice that adrenal adenomas producing epinephrine were reported infrequently as case reports. More importantly the injection of calcium containing IV infusions could have provoked the function of adenoma, as it appears that his diabetes and original HTN, were SECONDARY to the hormone producing NET.

As his disease was treated with Prazosin, and he lost weight, his DM was resolved. The magnificent response to Prazosin is diagnostic for pheochromocytomas, but negative metanephrines (with specificity of almost 100 percent) argues against the

diagnosis of pheo. That said the availability of NETest can be extremely helpful in these circumstances, as it becomes diagnostic gold standard in a case like this. We also believe that despite reliance on metanephrines in diagnosis of Pheo, the test carries significant bias, as it can be positive in patients who do not have pheo, such as patients taking proton pump inhibitors, or suffering from obstructive sleep apneas [2].

It is also hypothesized that the borderline hormone producing adenoma, is as common as the medical practitioners diagnose a " pseudo pheochromocytoma". If this theory is validated, it can change the way that medical providers approach this disease, as the old concept of neurotic, origin of the disease would be completely disputed. The traditional approach of using antidepressants for these patients and positive response to the treatment, also becomes a bias as all pheochromocytomas do get better with tricyclic antidepressants, as well.

Furthermore studies have shown that small cortical adenomas(less than 4 cm), are able to produce adrenaline(the electron microscopy of these adenomas cells reveal microgranules of epinephrine in the cells) Eränkö and Hänninen first described the coexistence of cortical and medullary features in adrenal cells in 1960, and terms such as mixed cells and corticomedullary cells have since been introduced [3-12].

This concept questions the anatomical classification of cortex and medulla in adrenal gland.

Unfortunately the advanced surgical techniques such as Partial adrenalectomy would fail to address these hormone producing adenomas, since they would continue to exist after classic partial adrenalectomy.(In the case presented the patient luckily refused such surgical approach) [13,14].

Conclusion

We suggest pseudo pheochromocytomas could all be adrenal functioning adenomas. These patients that have normal labs and can not be classified as functional adenomas, or pheochromocytomas, where in reality they are. This case also completely disputes the idea that positive metanephrines are needed for diagnosis of a small functional adenoma,. Interestingly also it becomes evident that small adrenal masses, can be extremely functional with life threatening presentation, yet with both normal labs and negative imaging. We conclude that adrenal adenomas uncharacterized otherwise and mislabeled as non functional could be the source of the hypertension and as such we should perform a liquid biopsy to detect the presence of neuroendocrine transcripts in the blood and if positive, an adrenalectomy on all cases of adrenal incidentalomas, whom clinically present with hypertension, not otherwise explained.

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