Case Report

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A Case of Pseudopheochromocytoma: Quetiapine Induction of Norepinephine

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ABSTRACT

An acutely altered elderly female presented following orthopedic repair. She was afebrile, normotensive, but tachycardic. Once declared medically stable, she was transferred to a geropsychiatric facility for stabilization of acute psychosis. Her psychosis remained refractory to treatment, and she was noted to have an elevated ionized calcium. Plasma metanephrines were evaluated, followed by confirmatory urinary metanephrines. Both were significantly elevated. Negative imaging following this laboratory workup prompted consideration of possible tertiary causes. It was determined that the patient was likely experiencing a phenomenon known as Pseudopheochromocytoma, induced by Seroquel, of which she was on the maximum recommended dose. Once Seroquel was discontinued, the patient's autonomic instability stabilized. Although a pheochromocytoma was not completely excluded by a PET scan in this case, its existence was unlikely, especially given autonomic improvement following Seroquel taper and discontinuation.

This case presents a unique opportunity for the Psychiatric and greater medical community to gain awareness about this rare phenomenon and be informed of this as a potential differential diagnosis. Pseudopheochromocytoma or pheochromocytoma in a psychotic patient are rarely considered, as autonomic instability must be concomitant. In this patient, an extensive work-up was carried out to exclude the diagnosis of a true pheochromocytoma, which must be done in any case in which psychosis with autonomic instability exists. While not exhaustive, the workup detailed in this case allowed for a conclusion to be reached, ultimately benefiting the outcome of the patient once the causative medication was discontinued.

Case Report

A 71-year-old Caucasian female with past medical history significant for bipolar I disorder previously well managed on 50mg Seroquel daily presented to an Emergency Department for acute altered mental status. She had no history of alcohol or illicit substance abuse, but notably was a former smoker. The patient had been a resident in a Skilled Nursing Facility following a lower extremity fracture requiring surgical repair. Prior to this fracture and subsequent rehabilitation, the patient had been at her baseline, living on her own, communicating appropriately, and able to complete her activities of daily life. In the Emergency Department, she was afebrile and normotensive. EKG in the Emergency Department was remarkable for sinus tachycardia with a rate of 114 bpm. History and physical performed by the consult liaison psychiatric team in the Emergency Department detailed the findings below.

Physical Exam

- **Constitutional:** Obese, conversant, chronically ill-appearing
- **Head:** Normocephalic, atraumatic'
- **Eyes:** Extraocular movement intact, pupils equal & round, sclerae anicteric
- **ENT:** Moist mucous membranes
- **Neck:** Supple, no thyromegaly
- **Respiratory:** Clear to auscultation bilaterally, symmetrical expansion
- **Cardiovascular:** Regular rhythm and rate
- **Gastrointestinal:** Soft, nontender, nondistended, normoactive bowel sounds, no masses
- **Musculoskeletal/Extremities:** No lower extremity edema, no cyanosis, no clubbing
- **Skin:** Warm & dry, no rash, intact
- **Neurologic:** No focal neurologic deficits, no hemiparesis
- **Psychiatric:** Awake, alert, odd affect

Vitals

- **Temperature:** 36.5 (oral)
- **Heart Rate:** 112
- **Respiratory Rate:** 19
- **Blood Pressure:** 112/67
- **SpO2:** 99% on 3.5L nasal cannula at baseline

Mental Status Exam

- **Appearance:** Disheveled
- **Behavior/Motor Activity:** Normal
- **Musculoskeletal:** Observed muscle strength/tone within normal limits
- **Gait/Station:** Not observed
- **Speech:** Pressured
- **Mood:** Fair
- **Affect:** Full
- **Thought Process/Associations:** Tangential, loose associations
- **Thought Content:** Visual hallucinations, delusional
- **Cognition/Attention/Memory/Concentration:** Alert & oriented x4, grossly intact attention, Memory – recent/ remote judged adequate by interview
- **Insight:** Impaired
- **Judgement:** Impaired
- **Language:** Within normal limits
- **Fund of Knowledge:** Adequate

Home Medications

Acetaminophen 650mg, oral, TID

Atorvastatin 40mg, oral, HS

Cholecalciferol 125mg, oral, daily

Clonidine 0.1mg, oral, Q6H, PRN

Diclofenac 1% topical gel, QID, PRN

Doxycycline 100mg, oral, daily

Trelegy Ellipta 100mcg-62.5mcg-25mcg/inh, 1 puff, inhalation, daily

DuoNeb 0.5mg-2.5mg/3mL inhalation solution, inhalation, QID, PRN

Metoprolol 12.5mg, oral, BID

Nicotine, 1 patch, topical, daily

Omeprazole 40mg, oral, daily

Lyrica 150mg, oral, TID

Quetiapine 50mg, chewed, HS

Simethicone 80mg, chewed, TID

Simethicone 20mg, oral, Q2H, PRN

The patient was initiated on treatment for a suspected UTI. She was declared medically stable for placement in an inpatient geropsychiatric facility 4 days after her Emergency Department presentation. Once the patient arrived in the geropsychiatric facility, her altered mental status, deemed to be acute psychosis, remained refractory to treatment. She also remained tachycardic, which had persisted throughout the entirety of her inpatient stay. Shortly after the patient's arrival in the geropsychiatric unit, it was noted that her calcium level was mildly elevated to 11.7 mg/dL (reference range 8.5-10.5 mg/dL). A PTH was drawn, showing a level of 36.2 pg/mL (reference range 15-50 pg/mL), a value well within the bounds of normal. Despite this unremarkable PTH, the patient's calcium remained consistently mildly elevated for 8 days (Figure 1), prompting further evaluation with an ionized calcium level. The first ionized calcium level for the patient was also consistent with mild elevation, at 5.7 mg/dL (reference range 4.5-5.3 mg/dL). This was trended with measurements four days apart, in which the mild elevation was sustained.

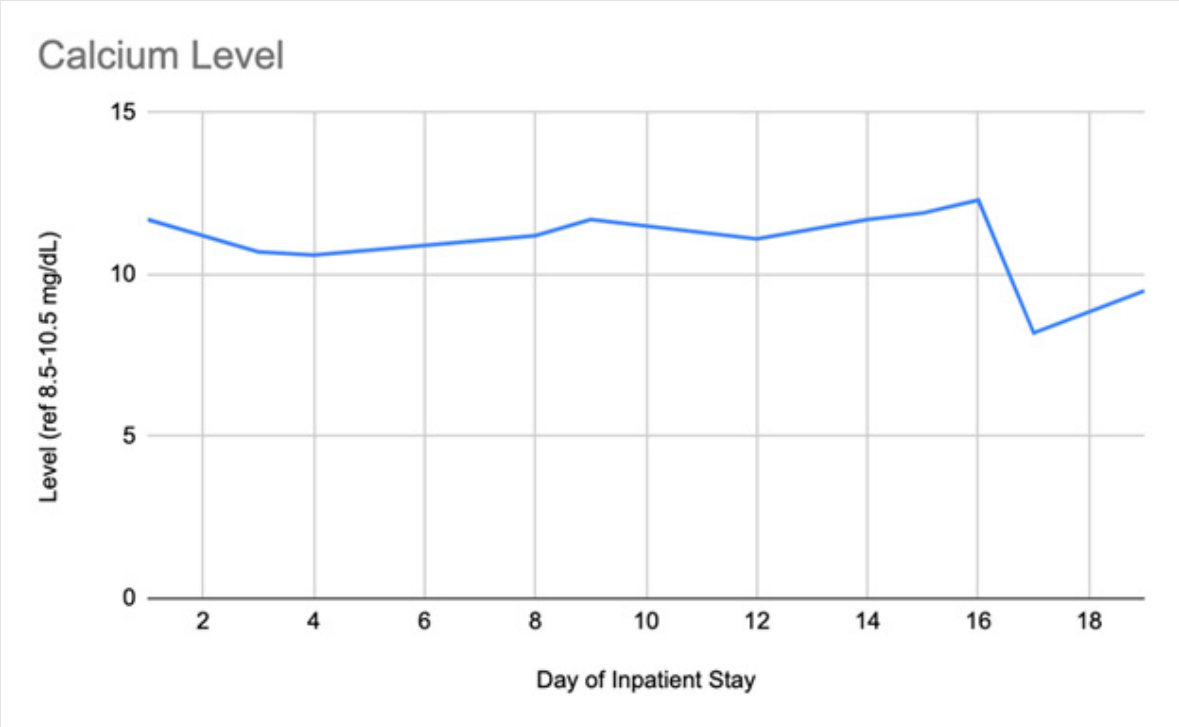

Figure 1: Patient's total serum calcium level, not ionized, trended during her inpatient stay.

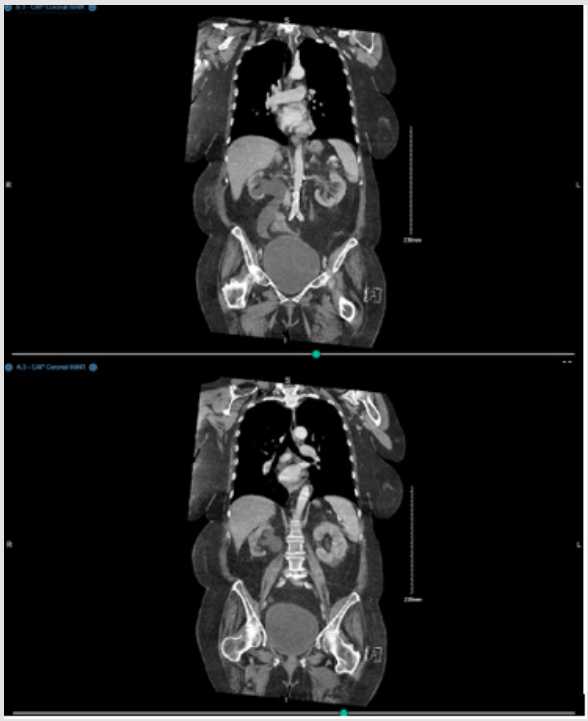

Figure 2: Selected images from the CT Abdomen and Pelvis with Contrast. Impression: Segmental pulmonary emboli most pronounced in the left lower lobe. No right heart strain. Severe right and mild left hydrouteronephrosis with a distended bladder. Punctate calculus in the distal left ureter. Multiple additional bilateral nonobstructing calculi. Right-sided cortical thinning. Dizziness change with bilateral pulmonary nodules. Consider comparison with remote priors versus short interval follow-up at 3 months.

To further evaluate this persistence in hypercalcemia, plasma metanephrines were obtained. These were also abnormal, with a level of 1.5 nmol/L (reference range <0.90 nmol/L). As clinicians, this raised the suspicion that an underlying paraneoplastic pathology was present. Endocrinology and Oncology were both consulted. Endocrinology services were unavailable at the facility, but Oncology assessed the patient and ordered imaging, laboratory studies, and an infusion of Zometa. While awaiting these labs, the Psychiatry team made the decision to order a 24-hour urine metanephrine study. The patient, still acutely psychotic and clinically worsening, tolerated the recommended imaging at that time. She was able to tolerate a CT of the abdomen, which was unremarkable for abdominal pathology, as seen in the report and images below (Figure 2).

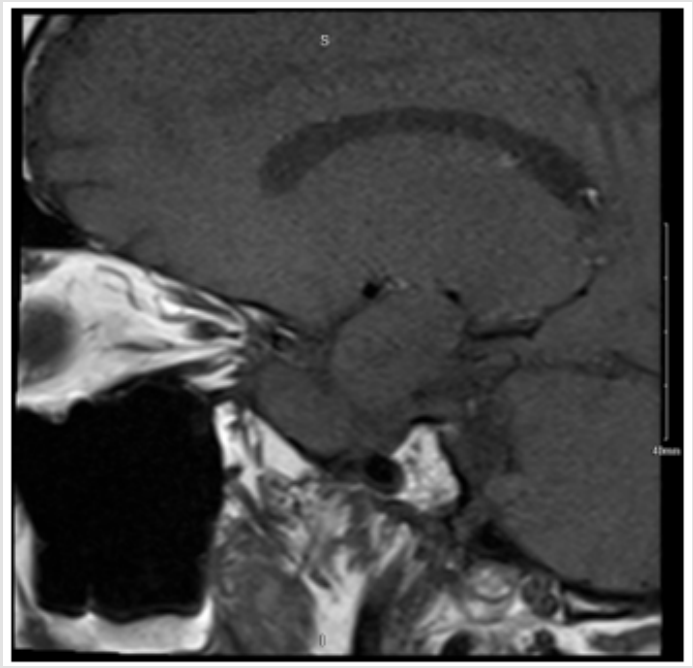

Figure 3: MRI of the patient's Brain. Impression: Normal appearance of the sella and pituitary. Please note that dynamic postcontrast sequences were not performed, such that a microadenoma is not excluded.

Oncology ordered lambda and kappa free light chain levels. Both of these levels were found to be elevated, with Kappa Free Light Chain at 4.00 mg/dL (reference range 0.33-1.94 mg/dL) and Lambda Free Light Chain at 3.78 mg/dL (reference range 0.57-2.63 md/dL). The patient's calcium had normalized with the infusion of Zometa, and had sustained this normalization for several days. With no remarkable imaging and a now stable calcium level, the Oncology service recommended the patient be discharged to follow-up with the outpatient oncology team for further evaluation. At this point, the patient's psychosis was continuing to worsen. Her dose of Seroquel had been increased to 600mg with no improvement in mental state. In fact, her mental status was worsening; with each evaluation, the patient became more tangential and was starting to ruminate on numbers. Tachycardia persisted. Hours after the Psychiatry team received the recommendation for discharge from the Oncology team, the patient's 24-hour urinary metanephrine panel resulted. The test results were remarkable, showing 1) Urine Metanephrines of 1102 mcg/24 hours (references range 30-180 mcg), 2) Urine Normetanephrines of 3886 mcg/24 hours (reference range 148-560 mcg), and 3) Total Metanephrines of 4988 mcg/24 hours (reference range 180-646 mcg). Oncology was called to consult again, and the differential of pheochromocytoma was introduced, prompting further imaging. This was discussed with her surrogate decision maker, who consented for the course of evaluation and care.

The patient's psychosis was only clinically worsening. MRI of the Brain and Abdomen were attempted multiple times, with the patient adamantly refusing. She was given Ativan, and finally cooperated for the MRI of the Brain, which was negative (Figure 3). Her Seroquel was increased to 800 mg, and she became increasingly more difficult to converse with, now ruminating on numbers most of the time. The patient continued to refuse MRI of the Abdomen, becoming restless and agitated with each attempt. Her psychosis continued

despite maximum recommended Seroquel dosing, so it was decided to discontinue Seroquel and start the patient on Clozapine. With a previously negative CT of the Abdomen performed only days prior, the care team made the decision to discontinue the order for the MRI of the Abdomen. At the point of discontinuation of the order for Abdominal MRI, the patient had been weaning off of Seroquel therapy for 2 days. Her tachycardia had resolved, and all medications for rate control had been discontinued. She was started on Clozapine. While a pheochromocytoma diagnosis cannot be completely excluded, the patient's negative imaging makes this extremely unlikely. The conclusion was reached that the patient's symptoms, while certainly consistent with possible pheochromocytoma, were instead induced by Seroquel. In the absence of imaging confirming the existence of a tumor, this effectively can be diagnosed as Pseudopheochromocytoma.

Discussion

Pheochromocytomas are chromaffin cell tumors which emerge from the neural crest. These tumors are typically neuroendocrine tumors mass producing catecholamines and detected by either serum fractioned metanephrines or urinary metanephrines [1]. These tumors are a rare phenomenon, with an annual incidence of 2 to 9.1 per 1 million adults but represent 60% of all adrenal incidentalomas [2]. Unfortunately, pheochromocytomas (pheos) can be missed likely secondary to the rare prevalence. This is underscored by The Mayo Clinic report of 54 autopsied patients whose pheos contributed to 55% of deaths and was not suspected in 75% of cases [3]. Pheos are typically either from random mutation or a manifestation of hereditary syndromes, which are inherited with autosomal dominant transmission [2]. Pheochromocytomas are considered the great masqueraders as they produce symptoms that can be explained by other disease processes. The symptoms are typically unearthed by a catecholamine surge. This excess catecholamine thus has downstream effects notably recognized as hypertension, tachycardia,and glucose dysregulation. Approximately 75% of patients later discovered to have pheochromocytomas died of cardiac arrest [4]. Unfortunately, there is no one set of clinical symptoms that are pathognomonic for pheos, nor do we have clinical findings to exclude pheo, which can be difficult when making a clinical determination for treatment. According to a recent Metanalysis, the greatest trend of symptoms associated with pheos included Hypertension (80%), Headache (60%), Palpitations (59%), and Diaphoresis (52%) [5]. Our case report included Tachycardia and unremitting psychosis. Although, at least two other case reports can be identified where psychosis was a primary sequela of pheo, it certainly is a rare manifestation and be quite difficult to manage.

James Brown records a case where psychosis remitted after pheochromocytoma was resected, considering that this may have been an anti-NMDA receptor tumor [6]. In this case, the psychosis was considered a paraneoplastic syndrome such as anti-NMDAR-E. This opens up the possibility that further examination of these tumors regarding their role in psychosis may contribute to the understanding of schizophrenia as a possible phenomenon of NMDA dysregulation [6]. In our case, the patient was suffering from treatment resistant psychosis. Kilani and others also report a case where an Adrenocortical Carcinoma was responsible for both panic attacks and psychosis [7]. Although not a pheochromocytoma, Kilani and others describe a neuroendocrine secreting carcinoma responsible for persistent psychiatric sequelae, including psychosis. In their case, the patient rapidly developed Cushing Disease with abnormal cortisol metabolism [7]. Interestingly, in a letter to the editor of the Journal of Endocrinology, Doogue and others claim to have treated a case of pseudo-pheochromocytoma, citing Seroquel as the cause of elevated urinary metanephrines. They cite Seroquel's mechanism of raising catecholamine levels is its direct antagonism of alpha-adrenergic receptors and to a lesser extent indirect dysregulation of norepinephrine reuptake [8]. Doogue notes that metanephrine values did not diminish after removal of tumor and did not de-escalate until Seroquel was withheld. Thus, could it be that Seroquel does antagonize norepinephrine re-uptake and as a result provides a false positive for urine metanephrines? [9] This is highly pertinent to our case as our patients was taking 800 mg of Seroquel at night for unremitting psychosis. She was eventually tapered from Seroquel therapy and started on Clozapine therapy for treatment resistant psychosis which apparently can also cause false positives or elevation of urine metanephrine levels [10].

In another case, Elman and others reported risperidone as having an indirect effect on plasma norepinephrine (NE) levels, but the mechanism behind this remains elusive. After investigation of risperidone, clozapine, and placebo, their data appears to suggest that both risperidone and clozapine elevate plasma NE levels via enhanced neurotransmitter spillover, not necessarily as a direct antagonism to norepinephrine reuptake [11].

A differential should be considered when assessing patients with uncontrolled diaphoresis, palpitations, and headache. The following table of diagnoses can be given consideration and would be helpful to rule out, particularly if urinary metanephrine excess is absent (Table 1). Now, given that our case is granted, unusual, it is not altogether impossible for there to be a dopamine secreting pheochromocytoma which could then theoretically produce an unremitting case of psychosis. [12] Primary dopamine secreting pheochromocytomas typically present with a patient who is normotensive, as in our case. There is also a concordant elevation of serum methoxytryamine levels, a metabolite of dopamine. Unfortunately, our hospital system did not have access to this particular lab test [12].

Table 1.

Differential Diagnoses [12]
Anxiety Disorder, including benzo withdrawal
Extra adrenal paraganglioma
Von Hippel-Linda-Disease
Essential Hypertension
Hyperthyroidism
Insulinoma
Mercury Poisoning
Paroxysmal Supraventricular Tachycardia
Renovascular Hypertension
Carcinoid
Baroreflex failure
Postural Tachycardia Syndrome
Sleep Apnea
Renal Failure
Pseudopheochromocytoma (severe paroxysmal hypertension)

CT is the radiograph often first utilized to identify a suspected pheo. The modality can detect a tumor >1mm in size with 87-100% sensitivity. But it should be noted that some tumors appear as cystic regions, calcifications, fibrosis, necrosis, and hemorrhage and as such are not always readily identifiable [13]. Remarkably, CT of the abdomen with contrast did not identify a tumor in our case. However, pulmonary nodules and incidental PE was detected when CT of Thorax was performed. Correction of pheochromocytoma is surgical removal of the tumor and life-long follow-up to monitor for re-emergence of tumor. Prior to surgery, alpha blockade can also assist in alleviating symptoms of uncontrolled hypertension, diaphoresis, and tachycardia. A clonidine suppression test can be implemented to evaluate whether plasma metanephrine levels diminish after an alpha antagonist.

Finally, given the absence of tumor on CT, we can only conclude that our patient's diagnosis was pseudopheochromocytoma secondary to Seroquel therapy resulting in false positive urine metanephrine analysis. Thus, mental health providers would do well to be aware of the possibility of elevated catecholamines associated with some atypical antipsychotics which particularly have high affinity for alpha adrenergic blockade and norepinephrine spill over which can ironically elevate catecholamines. Given the paucity of this effect in the literature, more case studies and pharmacology reviews can be helpful in order to avoid unnecessary work-up and imaging as well as tapering offensive agents which may be inducing somatic symptoms. Unfortunately, our patient refused MRI of abdomen and she did not go on to undertake a PET scan for a conclusive rule out of pheochromocytoma. Nonetheless, she did have a negative CT of the abdomen with no identifiable tumor, leading to our conclusions as above.

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