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Research Article

Paraneoplastic Limbic Encephalitis From a Carotid Body Paraganglioma Presenting as Persistent and Worsening Confusion

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Abstract

Background: Paraneoplastic Syndromes (PNS) are rare conditions in which patients experience a variety of symptoms from altered immune systems due to underlying malignancy. Paraneoplastic Limbic Encephalitis (PLE) is a subtype of PNS in which autoantibodies to cancer cells cross-react with cells in the central nervous system, particularly in the medial temporal lobe. Here we present a 38-year-old, previously normal male who presented with persistent and worsening confusion and was diagnosed with a very rare PLE secondary to a carotid body paraganglioma.

Case: A 38-year-old male with medical history of hypertension and polysubstance abuse was admitted initially for confusion, arm weakness, and memory loss. He denied having headache, fever, chills or neck stiffness. Further history obtained from family revealed he was previously cognitively intact. Imaging was consistent with carotid body paraganglioma and limbic encephalitis. A 5-day course of high dose steroids and plasmapheresis was initiated. Plasmapheresis was performed every other day for 5 treatments with marked improvement in mental and renal function at the time of the third treatment. Biopsies obtained were consistent with carotid body paraganglioma and surrounding lymphadenopathy was negative for disease. Embolization was performed with subsequent excision of the tumor and eventual resolution of symptoms.

Conclusion: This is to our knowledge the first documented case of paraneoplastic limbic encephalitis associated with a carotid body paraganglioma. Our patient had improved following resection of the underlying paraganglioma and experienced short-term improvement with high-dose steroids and plasmapheresis.

Keywords: Paraneoplastic Syndromes; Mental Confusion; Paraneoplastic Limbic Encephalitis

Introduction

Paraneoplastic Syndromes (PNS) are rare conditions in which patients experience a wide array of clinical sequelae from altered immune systems due to underlying malignancy generating antibodies, cytokines or hormones [1]. These second messengers may affect end organs in multiple organ systems and effects from paraneoplastic syndromes may be felt prior to awareness or diagnosis of the culprit malignancy, making early identification crucial for prompt initiation of treatment [1]. Certain paraneoplastic syndromes have well described clinical associations such as myasthenia gravis from acetylcholine receptor antibodies from thymoma or Lambert-Eaton myasthenic syndrome from small-cell lung cancer [2,3]. The majority of paragangliomas follow an indolent course and remain benign. However, a minority of cases may transform to have metastatic spread [4]. One subtype of paraneoplastic syndrome is paraneoplastic limbic encephalitis in which autoantibodies to cancer cells cross-react with cells in the central nervous system, specifically those in the medial temporal lobe [5]. Symptoms of this condition may include changes in personality, memory loss, hallucinations or seizures [5]. Antineuronal antibodies seen in paraneoplastic

syndromes such as limbic encephalitis include anti-Hu, anti-Ta, anti-Ma [6].

Here, we present a 38-year old, previously normal male who presented to the emergency room with persistent and worsening confusion and was eventually diagnosed with a very rare paraneoplastic limbic encephalitis secondary to a carotid body paraganglioma. This is to our knowledge the first documented case of paraneoplastic limbic encephalitis or encephalomyelitis associated with a carotid body paraganglioma.

Ethical Statement

the project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Case Presentation

A 38-year-old male with a known past medical history of hypertension and polysubstance abuse (cannabis and stimulant use) was admitted initially due to confusion "for the past few days" per the patient. The patient stated that he had not been acting like himself and his memory had been very poor. On further questioning about the symptom onset the patient stated that he "might've had the symptoms for a while"but he was unable to further clarify his history or answer most questions. He stated he was also concerned that he was having a stroke as he had on-and-off weakness of his left arm with some lightheadedness but denied other complaints including headache, nausea, vomiting, fever, chills or neck stiffness. He similarly denied any other neurological deficits except for his new left arm weakness. Further history obtained from his mother revealed that the patient had been living independently to this point and was previously cognitively intact. She observed that the patient appeared to be progressively more confused over the previous 2-3 weeks and recalled erratic behavior and anger issues over the previous year. The mother also states he had also been recently complaining of dysphagia and difficulty breathing.

On admission to the Emergency Department, the patient was hypertensive at 162/99 mmHg. Vitals on admission were otherwise unremarkable and the patient was afebrile. Physical exam was significant only for 3/5 left upper extremity weakness and orientation only to self. No nuchal rigidity, Kernig or Brudzinski sign was appreciated. Initial laboratory analysis significant for elevated White Blood Cell count (WBC) of 12.3 x103 uL (4.4-10.5 x103 uL) and mild microcytic anemia. Further labs such as ammonia, Thyroid Stimulating Hormone (TSH), Vitamin B1, B12, and folate was normal. HIV and Rapid Plasm Reagin (RPR) were negative. Urine drug screen was positive for cannabinoids alone.

A Computed Tomographic (CT) scan of the head without contrast was obtained and revealed a questionable subtle hypodensity in the right temporal lobe and a right soft tissue density mass at the superior aspect of the right carotid region. CT scan of the neck with contrast was obtained to further characterize the mass, revealing avidly enhancing 3.9 x 4.4 x 4.9 cm mass at the right carotid bifurcation with prominent adjacent lymph nodes consistent with paraganglioma as seen in Fig. 1. The carotid artery was nearly completely encased and the mass was seen to have splayed the internal and external carotid arteries with internal jugular vein compression. The mass effect appreciated on this imaging prompted CT angiogram of the head and neck which revealed patent carotid and vertebral artery circulation and continued to demonstrate internal jugular vein compression. Urine and plasma metanephrines were ordered and were significant for elevated supine plasma norepinephrine at 836 pg/mL (70-750 pg/mL), elevated plasma dopamine at 48 pg/mL (<30), elevated normotensive normetanephrine/creatinine and total normotensive metanephrine/creatinine at 405 (60-216) and 473 (106-312). Free metanephrines were normal.

Brain and neck MRI without contrast was obtained showing enhancement in the bilateral hippocampi and medial temporal lobes with additional multiple small foci of scattered patchy subcortical enhancement in the bilateral cerebral hemispheres most suspicious for autoimmune/limbic encephalitis as seen in Fig. 2. Carotid body findings were redemonstrated on this MRI along with lymphadenopathy. DOTATATE PET/CT scan was obtained with the neck mass being intensely tracer avid consistent with somatostatin receptor positive disease as seen in Fig. 3. A multi-specialty team of physicians were involved in the management of this case including neurology, oncology, head and neck surgery, infectious disease, nephrology, neurosurgery, neuroradiation oncology, and vascular surgery.

Continuous video Electroencephalography (cEEG) was performed revealing three left temporal electrographic seizures and abundant left temporal sharp waves in 24 hours. This prompted initiation of empiric treatment with acyclovir for suspected HSV as well as levetiracetam. Lumbar puncture was performed with colorless, clear Cerebrospinal Fluid (CSF) drawn. WBC and RBC count was elevated at 34 (0-5/uL) and 36 (0-0/uL) respectively. CSF neutrophil percentage was elevated at 16% (reference range ≤6%) and CSF lymphocyte percentage was normal 52% (reference range 40-80%). Glucose and protein were normal at 62 (40-70 mg/dL) and 40 (15-45 mg/dL). CSF culture did not grow any pathogens. Full meningitis and encephalitis panel returned negative including cryptococcal antigen, HSV 1 and 2, Lyme, West Nile virus, EBV, CMV, JC virus, and HHV6. Karius panel was performed without pertinent findings. Entire encephalopathy autoimmune panel, paraneoplastic antibody panel, rheumatological panel, arbovirus antibody panel, demyelinating disease panel, GAD65 antibody, and CSF Oligoclonal banding, all returned negative.

Acyclovir was discontinued due to negative infectious disease work up. Levetiracetam was changed to valproic acid shortly after initiation due to continued behavioral disturbances. He was started on a 5-day course of IV methylprednisolone 1000 mg daily due to radiographic and clinical evidence for limbic encephalitis. Plasmapheresis was started and he was treated every other day for a 5-treatment course resulting in significantly improved mental status and renal function at the time of the third treatment. The patient was discharged with follow up instructions and medications but was readmitted shortly afterward with worsened confusion. MRI brain revealed similar changes to prior MRI. The mass and surrounding lymphadenopathy were biopsied. Surrounding lymph nodes were negative for tumor presence and the carotid body tumor pathology was consistent with paraganglioma. The tumor was positive for chromogranin and synaptophysin, with patchy positivity for S-100 and GATA-3. The decision was made to undergo carotid body tumor embolization as extensive work up for other etiologies returned negative. The patient was started on alpha blockade with phenoxybenzamine 10 mg BID for pre-op preparation to mitigate perioperative catecholamine surge.

Embolization of the carotid body tumor was performed followed by neck exploration and excision of the right carotid body tumor. Stump ligation of the external carotid artery system was performed due to extensive tumor involvement. The patient initially did well however develop a right neck hematoma the next morning requiring emergent re-exploration, finding that the internal carotid had virtually disintegrated. Interposition bypass graft was successfully performed. The patient following this had fluctuant mental status from delirium that ultimately improved. The patient eventually was weaned off of ventilation support and was discharged to a skilled nursing facility. Histopathology of the tumor was consistent with carotid body paraganglioma and previous findings on biopsy.

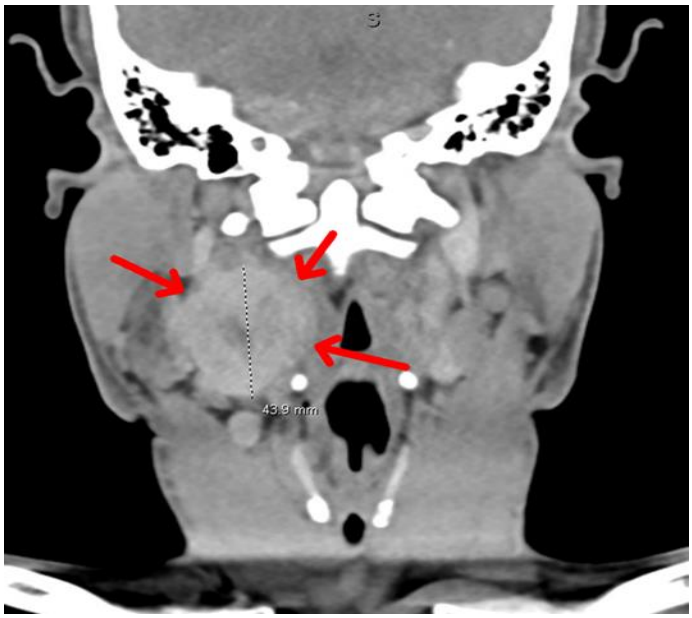

Figure 1: Coronal CT imaging revealing right-sided 3.9 x 4.4 x 4.9 cm carotid body paraganglioma (red arrows) with lymphadenopathy and mass effect on surrounding structures.

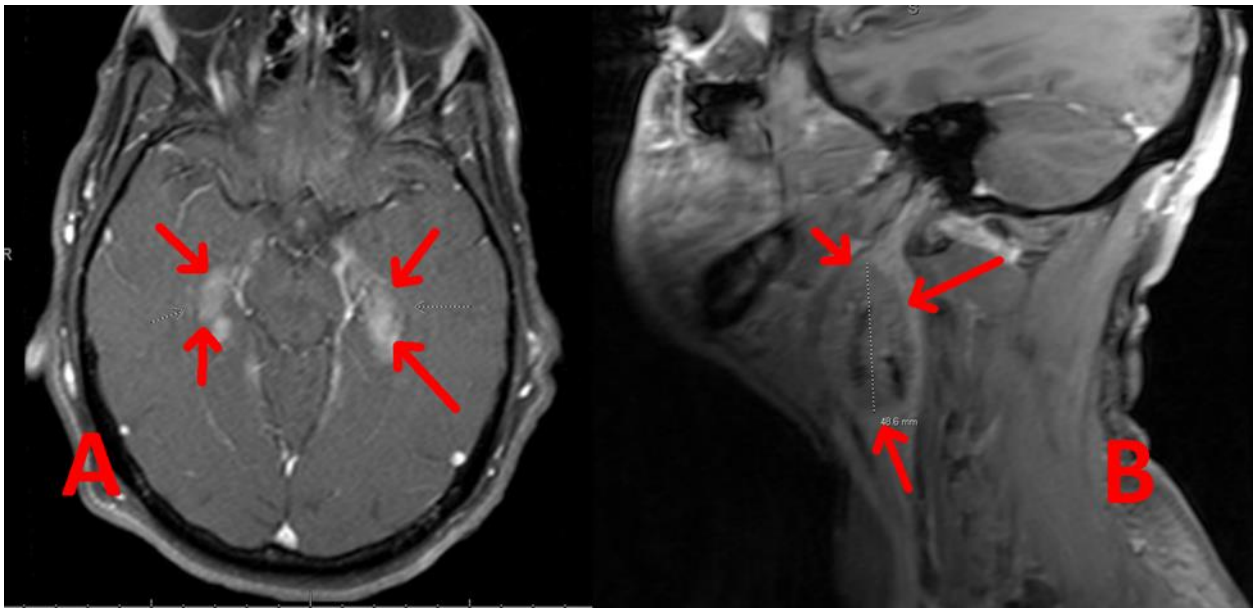

Figure 2: Noncontrast MRI imaging of the brain A (cross-section) and B (sagittal) revealing enhancement in bilateral hippocampi and medial temporal lobes (red arrows). Multiple small foci of scattered patchy subcortical enhancement in the bilateral cerebral hemispheres, suspicious for autoimmune/limbic encephalitis. Redemonstration of carotid body paraganglioma.

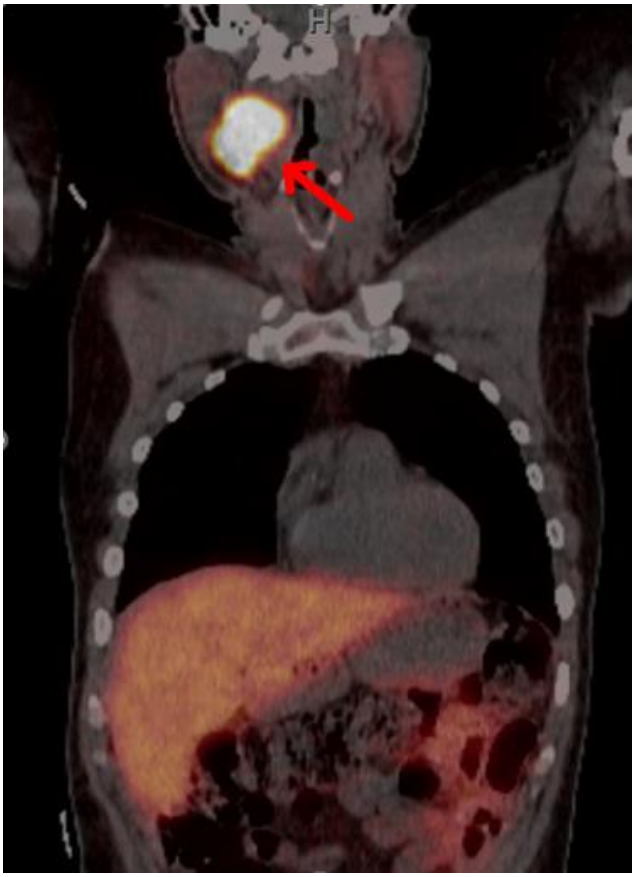

Figure 3: Coronal PET/CT imaging redemonstrating right-sided carotid body paraganglioma and lymphadenopathy and showing intensely tracer avid tumor consistent with somatostatin receptor positive disease. Tracer avidity noted by intensity of red-orange glow (red arrow), with brighter areas noting high avidity and uptake or tracer. PET/CT is sensitive for neuroendocrine tumors such as the one in our case.

Discussion

Paragangliomas are rare tumors made up of cells and tissues of sympathetic or parasympathetic paraganglionic origin [7]. Embryologically, paraganglionic tissue are made of neuroendocrine cells of neural crest cells origin. Neural crest cells are pluripotent cells that result in a great number of cell types within the central nervous system, autonomic nervous system, and other hybrid cell types that interface neural cells with the rest of the body via neurohormonal mechanisms [8]. The majority of sympathetic paragangliomas such as pheochromocytomas arise in the adrenal glands and the abdomen, the location of many sympathetic paraganglia, while parasympathetic paragangliomas are most likely to arise in the head and neck [9]. One of the most common locations for parasympathetic paragangliomas to develop is the carotid body, a parasympathetic paraganglia located at the bifurcation of the internal and external carotid artery that plays an important role in blood pressure regulation [9]. Intuitively, other sites of parasympathetic paragangliomas are other sites of expected parasympathetic activity such as vagal and laryngeal paragangliomas, however these are exceedingly rare tumor types. Clival paragangliomas are another rare subtype of paraganglioma which may arise near the clivus, an area at the base of the skull [10]. This is another area of high parasympathetic activity due to the number of cranial nerves that run through the area and clinicians should keep clival paragangliomas on their differential when diagnosing tumors at the skull base [10].

Carotid body paragangliomas have gone by many names, including glomus tumors, chemodectomas, and non-chromaffin tumors [11]. Despite being active neurohormonal structures, paraneoplastic syndromes in paragangliomas have not been well described in the literature likely due to the lack of reported cases due to rarity of both conditions independently of reportedly only 2-8 cases per million for paragangliomas and PNS incidence of 0.8/100,000 person-years in some studies [1,12,13].

Paraneoplastic syndromes are a curious family of conditions as a causal mechanism for their development has not been well described [1]. Though there are strong associations of certain cancers and respective syndromes it is still possible for paraneoplastic syndromes to arise in any malignancy, however unlikely [1]. Paraneoplastic limbic encephalitis is usually associated with lung cancer, lymphomas, bladder cancer, testicular cancer, breast cancer, thymoma and teratoma [6,14]. Study of the different onconeuronal antibodies that are causative of limbic encephalitis is ongoing with commonly associated antibodies being anti-Hu, anti-Ta, anti-Ma, anti-GABA(B) which is often found in anti-Hu negative small-cell lung cancer or anti-mGLuR5 associated with Ophelia syndrome in Hodgkin lymphoma [6,15]. Our patient lacked any classical antibodies and all panels were negative. It should be noted that diagnosis of paraneoplastic limbic encephalitis is not reliant on antibody positivity as antibody panels have low sensitivity and controversial clinical utility and the antibodies are sometimes more closely associated with limbic encephalitis associated tumors than limbic encephalitis itself [16]. CNS symptoms from paraneoplastic limbic encephalitis or encephalomyelitis uncommonly may result in endocrine derangements from damage to the hypothalamus but are otherwise intuitive including short term memory loss, personality changes, hallucinations or seizures [1,5].

This case was a significant diagnostic and treatment challenge due to the lack of previous reports. Treatment was guided based on principles gleaned from other somewhat related case reports for paraneoplastic syndromes in paragangliomas such as one such case illustrating disappearance of epilepsy following resection of an extra-adrenal paraganglioma [17]. Additionally, there have been recorded instances instances of psychosis resolving after treatment of underlying pheochromocytomas, a sympathetic paraganglioma [18]. Despite extensive literature review no single case was found to match our patient's presentation. There are multiple initial treatment options of limbic encephalitis such as high-dose corticosteroid treatment and plasma exchange as employed in our patient's case, but may also include IVIG or certain steroid-sparing immunosuppressives [19]. Bortezomib is a treatment option in anti-NMDA antibody positive disease [19]. Paraneoplastic limbic encephalitis and encephalomyelitis has been reported to resolve with treatment of the primary cancer although improvement may be gradual [19]. Paraneoplastic limbic encephalitis arising in patients with paragangliomas raises an interesting conundrum as confusion may be secondary to or worsened by catecholamine-induced psychosis or confusion from excess hormone released by the paraganglioma itself. As carotid body tumors are rarely malignant and usually ideal surgical candidates, we chose to pursue surgical resection once metastasis was ruled out. Surgical approaches continue to improve due to advancements in technology such as Augmented Reality (AR) [20]. Due to the intimate nature of carotid body paragangliomas with vital structures such as the carotid bifurcation and both carotid arteries, AR surgical planning and navigation may become more widely accepted for these tumor types [20].

Conclusion

This is to our knowledge the first documented case of paraneoplastic limbic encephalitis or encephalomyelitis associated with a carotid body paraganglioma. Our patient had antibody-negative disease with improvement of symptoms following resection of the underlying paraganglioma and short-term symptomatics improvement with high-dose steroids and plasmapheresis. Carotid body tumors are rarely malignant and if surgical resection is possible it is preferred. Paraneoplastic syndromes can manifest in a number of different ways and may occur in any cancer, even those that are not classically associated.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Acknowledgement

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Financial Disclosure

None to disclose

Data Availability

All data underlying the results are available as part of the article and no additional source data are required.

Author's Contribution

The authors contributed equally in the preparation of this manuscript.

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