International Journal of Cerebrovascular Disease and Stroke
Tausinga T et al. Int J Cerebrovasc Dis Stroke 6: 167.
www.doi.org/10.29011/2688-8734.000067
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Case Report

Paraneoplastic Syndrome Masquerading as Recurrent Cerebellar Vascular Injury: A Case Report

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Citation: Tausinga T, Asadian M, Singh M (2023) Paraneoplastic Syndrome Masquerading as Recurrent Cerebellar Vascular Injury: A Case Report. Int J Cerebrovasc Dis Stroke 6: 167. DOI: https://doi.org/10.29011/2688-8734.100167

Received Date: 06 November, 2023**; Accepted Date:** 11 November, 2023**; Published Date:** 14 November, 2023

Abstract

Stroke is second leading cause of death and disability worldwide. Thus, it is critical to perform prompt workups when patients present with the concerning signs and symptoms. However, many other medical conditions mimic stroke and can account for hospitalizations where stroke and vascular workups are pursued, oftentimes being costly not only to the patient but to the medical system. One category of under recognized mimics is paraneoplastic neurologic syndromes, which are a variety of neurologic disorders associated with systemic malignancy. Kelch-like protein 11 antibody is a recently discovered antibody associated with paraneoplastic neurologic syndromes. Herein, we present a unique case of a patient presenting with recurrent and persistent cerebellar stroke-like symptoms found to have an underlying Kelch-like protein 11 antibody-associated paraneoplastic syndrome. We review the entirety of his presentation, review the current literature on this paraneoplastic syndrome, and discuss implications from this case that can be applied in future practice.

Introduction

Kelch-like protein 11 antibody-associated paraneoplastic syndrome (KLHL 11 PNS) is a novel autoimmune-driven process typically associated with malignancy. Approximately 90 patients with KLHL 11 PNS have been reported in the literature since the first case was described in 2019 [1,2]. These studies note that KLHL 11 PNS is most often characterized by brainstem and cerebellar involvement, both of which are common targets of paraneoplastic autoimmunity in this syndrome. Patients may present with gait instability, diplopia, and vertigo, with exam findings notable for dysmetria, nystagmus, nuclear or supranuclear gaze palsy, and dysarthria [1].

KLHL 11 PNS has a strong oncological association with testicular germ cell tumors (TGCT) seen in 78.7% cases, particularly seminoma seen in 54.1% cases. Cases involving small-cell lung cancer, lung adenocarcinoma, ovarian carcinoma, ovarian teratoma, laryngeal SCC and chronic lymphocytic leukemia have also been described [1,2]. Due to the rarity and novelty of KLHL 11 PNS, exact epidemiological data are still lacking, and its clinical spectrum is continually evolving. In this case report, we describe a unique presentation of KLHL 11 PNS in a patient with progressive stroke-like symptoms associated with underlying malignancy.

Case Presentation

A 69-year-old male with a past medical history of hypertension, pre-diabetes, coronary artery disease, and a recent diagnosis of prurigo nodularis several weeks prior, presented to the emergency department (ED) due to subacute onset of slurred speech, unsteady gait, dizziness, frequent falls, and unintentional weight loss of 28 kg over two months. Examination was remarkable for reduced vibration sense in bilateral lower extremities and extensive ulcerating rash on his neck and upper chest (**Figure 1**). Laboratory findings were significant for a low vitamin B12 level, microcytic anemia, hypokalemia, and hypomagnesemia (**Table 1**). B12 and electrolyte supplementation were provided without

improvement. Magnetic resonance imaging (MRI) brain without contrast showed evidence of remote left superior cerebellar insult. (Figures 2,3). Inpatient admission was considered for further evaluation, however the patient strongly requested discharge. Thus, a plan was made for close patient follow-up with neurology and physical therapy.

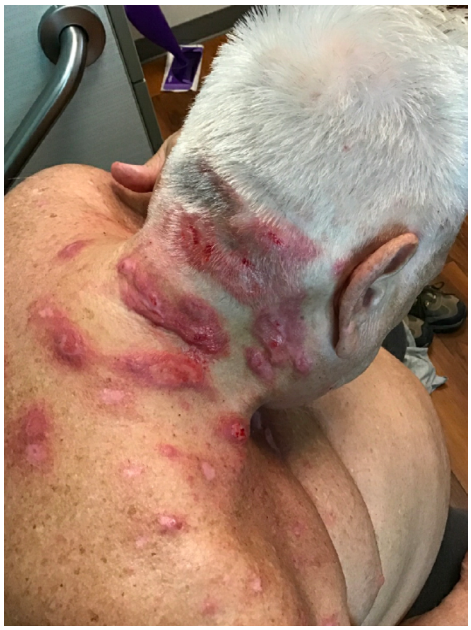

Figure 1: Prurigo nodularis on initial presentation.

	Value	Reference Range
Sodium	134 (L)	136 – 144 mmol/L
Potassium	2.8 (L)	3.3 - 5.0 mmol/L
Chloride	98 (L)	102 - 110 mmol/L
Carbon Dioxide	24	20 - 26 mmol/L
Blood Urea Nitrogen (BUN)	11	8 - 24 mg/dL
Creatinine	0.54 (L)	0.72 - 1.25 mg/dL
Glucose	96	64 - 128 mg/dL
Calcium	9.0	8.4 - 10.5 mg/dL
Albumin	3.1 (L)	3.5 - 5.0 g/dL
White blood count (WBC)	11.32 (H)	4.30 - 11.30 k/uL
Hemoglobin	10.1 (L)	14.8 - 17.8 g/dL
Hematocrit	32.7 (L)	44.2 - 53.0 %
Platelets	355	159 - 439 k/uL
Mean corpuscular volume (MCV)	75.3 (L)	81.2 - 96.6 fL
Hemoglobin A1c	6.1 (H)	<=5.6 %
Magnesium	1.4 (L)	1.6 - 2.6 mg/dL
Erythrocyte sedimentation rate (ESR)	56 (H)	0 - 10 mm/hr
C-reactive protein (CRP)	12.6 (H)	0.0 - 0.8 mg/dL
Vitamin B1	60 (L)	70 - 180 nmol/L

Vitamin B6	13.2 (L)	20.0 - 125.0 nmol/L
Vitamin B12	177 (L)	180 - 914 pg/mL

Table 1: Obtained on initial presentation. All other labs were unremarkable including complete blood count (CBC) with differential, remainder of complete metabolic panel (CMP), urine toxicology and urinalysis.

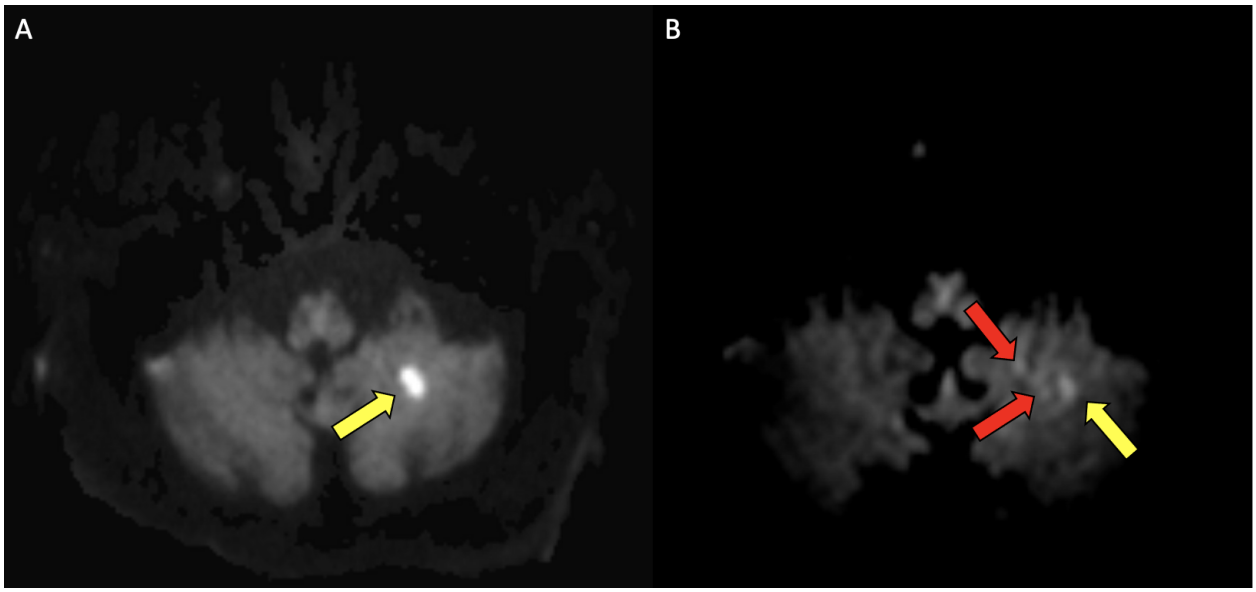

Figure 2: MRI of the brain at presentation (A) demonstrates area of restricted diffusion in the left cerebellar hemisphere (yellow arrow). MRI of the brain one month later (B) demonstrates stippled new areas of restricted diffusion (red arrows) adjacent to the original lesion (yellow arrow).

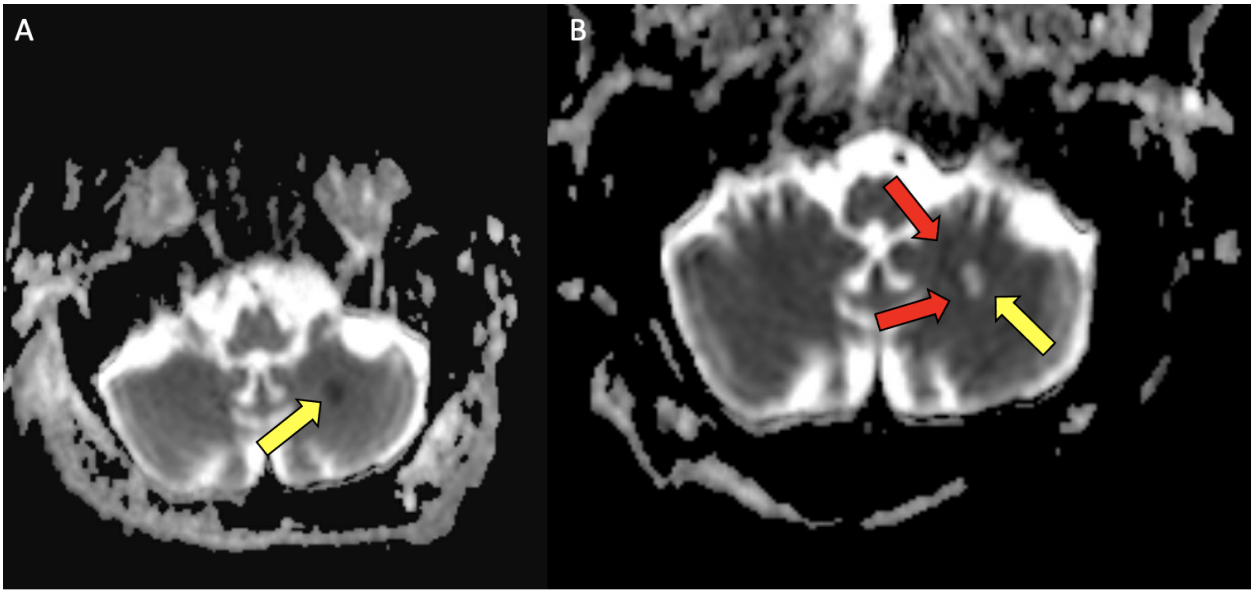

Figure 3: MRI ADC imaging of the brain at presentation (A) demonstrates area of restricted diffusion in the left cerebellar hemisphere (yellow arrow). MRI of the brain one month later (B) demonstrates stippled new areas of restricted diffusion (red arrows) adjacent to the original lesion (yellow arrow).

The patient presented to the ED one month later with persistent neurological symptoms and increasing falls at home. His evaluation was significant for severe dysarthria, mild dysmetria on finger-to-nose, dysmetria on heel-to-shin testing, and positive Babinski on the right. An MRI brain with and without IV contrast showed a remote infarct within the left inferior cerebellar hemisphere which had been previously identified however multiple acute infarctions were present throughout the surrounding area concerning for recent cerebellar infarct (Figures 2,3). The neurology team was again involved. The patient was not a candidate for tissue plasminogen activator (tPA) or endovascular therapy based on time of symptom onset and was therefore started on aspirin and a statin. A vasculitis panel was unremarkable outside of a positive ANA, telemetry showed normal sinus rhythm and an echocardiogram with bubble study was within normal limits. After neurological work-up, patient was discharged to a rehabilitation facility.

The patient presented to the ED three weeks later from his facility with new acute right-sided weakness. His physical exam revealed dysarthria, dysmetria and overall generalized symmetric weakness in all extremities. A repeat MRI brain showed no new areas infarct, though analysis was limited by patient motion artifact. However, computed tomography angiography (CTA) head and neck imaging obtained during further neurological workup revealed a 5.5 cm multi-cystic and solid mass in the right posterior cervical space (**Figures 4,5**), with pathology revealing a non-keratinizing squamous cell carcinoma (NKSCC) with p63 and p16 positivity (**Figures 6,7**). CT abdomen and pelvis was unremarkable. Positron emission tomography (PET) scan was notable for F-fluorodeoxyglucose (FDG) avid right neck mass and lymph nodes, indicating areas of metabolically active malignant lesions. The patient's recurrent and progressive neurologic and dermatologic symptoms leading to third hospitalization within a span of three months being uncharacteristic of secondary to stroke, diagnostic consideration was given to a paraneoplastic syndrome mimicking stroke. Cerebrospinal fluid (CSF) studies were obtained and revealed lymphocytic pleocytosis (**Table 2**). Serum and CSF studies evaluating for encephalopathy, autoimmune and paraneoplastic processes (ENC/ENS Mayo panel) were also obtained, with CSF confirming the presence of the KLHL 11 antibody. Literature review revealed that KLHL 11 antibody has been associated with cerebellar PNS and might resemble acute and subacute infarct on imaging. As such, PNS was deemed the driving diagnosis rather than stroke. The patient's consistently worsening prurigo nodularis was also diagnosed as another paraneoplastic element to his presentation.

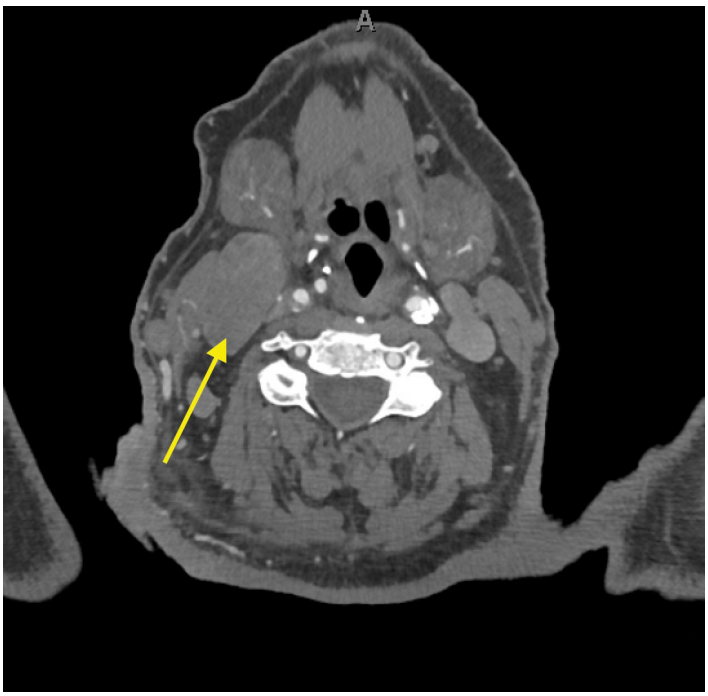

Figure 4: Axial CTA head and neck showing a 5.5 cm multi-cystic and solid mass in the right posterior cervical space.

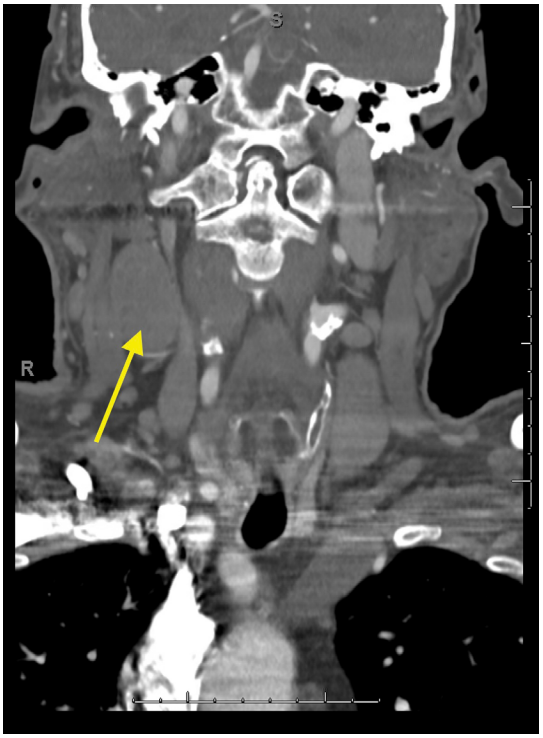

Figure 5: Coronal CTA head and neck showing a 5.5 cm multi-cystic and solid mass in the right posterior cervical space.

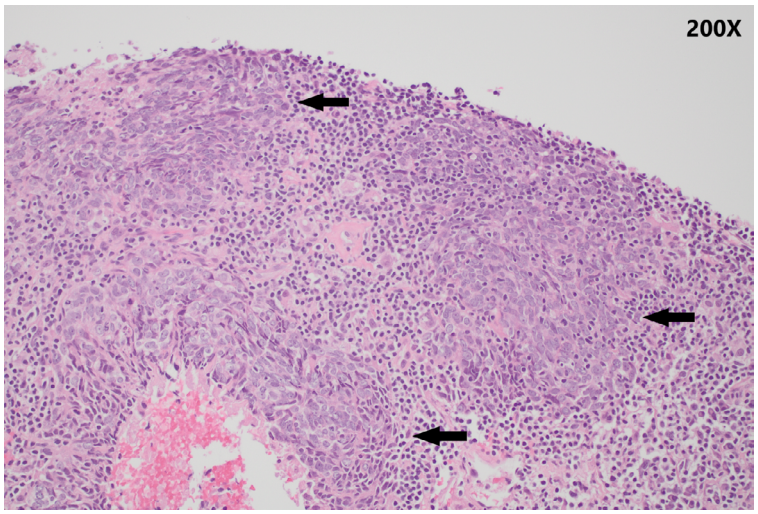

Figure 6: A core needle biopsy of a cervical lymph node demonstrating a nonkeratinizing squamous cell carcinoma (black arrows) involving the lymph node at 200X magnification (H&E stain).

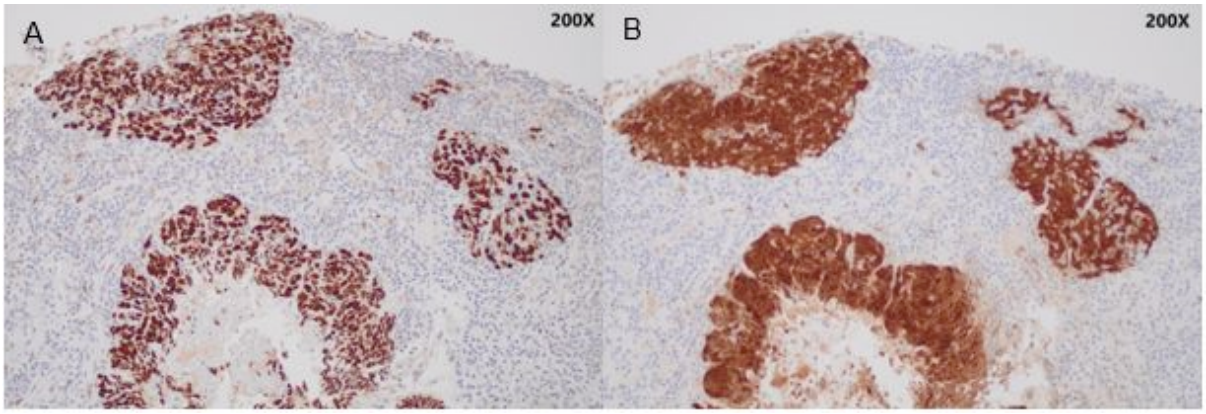

Figure 7: Tumor cells are strongly and diffusely positive for p63 (A) and p16 (B) immunohistochemical stain (200X).

	Value	Reference Range
CSF		
Appearance	Clear	Clear
Color	Colorless	Colorless
Protein, total	41	14 - 45 mg/dL
Glucose	88 (H)	50 - 80 mg/dL
Immunoglobulin G	1725 (H)	768 - 1632 mg/dL
Oligoclonal Bands	Positive	Negative
KLHL11 Ab IFA Titer	1:1920 (H)	Positive titer <1:240

Table 2: Obtained during PNS work-up. All other labs were remarkable, including Venereal disease research laboratory test (VDRL) CSF Reflex, varicella-zoster virus (VZV) antibody CSF, Antineutrophilic cytoplasmic antibody (ANCA) Immunofluorescence assay (IFA), human immunodeficiency virus (HIV), Muscle-specific tyrosine kinase (MuSK) antibody, Ganglioside antibody, serum protein electrophoresis, and remainder of ENC/ENS Mayo panel.

Due to KLHL 11 PNS's known association with TGCT in literature, the patient underwent testicular ultrasound and serum beta-human chorionic gonadotropins (ß-HCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH) were collected, all of which were unremarkable. The patient was treated with a 5-day course of intravenous steroids, intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) with no significant improvement in symptoms. The patient underwent right neck dissection with the removal of a 5.7 cm tumor, right radical tonsillectomy, and right base of tongue resection without surgical complications. He was subsequently initiated on a cyclophosphamide infusion for PNS with plans to continue them monthly for treatment, and radiation. The patient also began treatment with a targeted agent for underlying malignancy but stopped shortly after initiation due to the severity of side effects. Over the next several months, the patient had mild improvement in PNS symptoms.

Discussion

Stroke is one of the leading causes of morbidity and mortality globally. Furthermore, in the United States, the economic burden of stroke is estimated to be over $890 billion annually, with delays in care leading to poorer patient outcomes [3]. As stroke mimics account for over half of the hospitalizations for stroke and vascular workups, it is imperative to consider stroke mimics and other etiologies for stroke-like symptoms upon a patient's initial presentation [2]. In the case described above, stroke mimics considered in the initial differential diagnosis included hypoglycemia, nutritional deficiencies (such as B12 and thiamine), Guillain-Barre Syndrome, inflammatory myopathies, endocrine disorders, and other autoimmune processes (such as Myasthenia Gravis). Initial lab work was not suggestive of these diagnoses, and as imaging findings were congruent with remote cerebrovascular accident, further workup for other stroke mimics was not pursued. The severity, chronicity, and progression of neurological symptoms continued over the coming months, which led to additional stroke workup and incidental discovery of the right neck mass. This mass, found two months after the patient's initial presentation, prompted inclusion of PNS in the differential diagnosis.

PNS comprise a group of paraneoplastic disorders resulting from abnormal immune responses originating from underlying malignancy, and they often affect areas of the body distant from the original tumor. PNS affect as many as 8% of cancer patients and are often the first clinical manifestation of symptomology before cancer diagnosis, even in cases with minimal tumor growth [4]. Neurologic PNS occur in 1 % cases with malignancy, and up to 12.5% of cases with Head and Neck malignancies [5]. PNS often involve the central nervous system and present with neurologic findings that resemble stroke [6]. Since the discovery of the first neuronal antibody in 1960, various antibodies have been associated with PNS, with the KLHL 11 antibody first being cited in the literature in 2019 [2]. The precise mechanism of KLHL 11 PNS remains unclear. KLHL 11 is an intracellular protein ubiquitin ligase, and KLHL IgG may be involved with T-cell receptor recognition and cytotoxic injury [7]. Neuropathological studies have revealed that KLHL 11 antibody's role in T cell-mediated immunological effects may contribute to lymphocytic infiltration in the brain and lead to progressive, irreversible neuronal loss. KLHL 11 PNS may also be linked to neoplasms with underlying autoimmunity and human leukocyte antigen (HLA) genetic predisposition. Furthermore, KLHL 11 PNS is strongly associated with symptoms of cerebellar defects, such as in the case described above. Neuroimaging may resemble stroke and primarily show hyperintensities on T2/ fluid-attenuated inversion recovery (FLAIR) sequences in the temporal lobe, cerebellum, and brainstem [2].

PNS in general are associated with progressive disability and poor prognosis, including in KLHL 11 PNS patients [8]. In the limited cases of KLHL 11 PNS reported, it is shown that the onset of neurological symptoms preceded tumor detection by an average of six months. Tumors were ultimately detected in 73.5% of patients, with TGCT being the most common. While there is no standard management strategy for KLHL 11 PNS, early initiation of aggressive immunotherapeutic agents and oncological management may improve prognosis. However, in one analysis progressive neurological function decline occurred in 48% of patients with KLHL 11 PNS despite treatment, with over 58% of patients requiring gait aid (such as wheelchair or roller walker) in follow-up visits ranging from 2 to 216 months after diagnosis [1]. With aggressive treatment, 23% of patient's neurological status stabilized, and 29% had an overall improvement of neurological status. The median survival time from onset of symptoms for KLHL 11 PNS has been reported to be 55 months, with most causes of mortality linked to neurological deficits (such as bleeding from falls or bulbar involvement) rather than tumor burden [1]. As illustrated in our case, the patient's continual neurological decline posed a significant risk to his life with multiple falls reported at home. After his KLHL 11 PNS diagnosis and subsequent tumor resection, the patient was able to connect to needed resources to limit his fall risk and ensure a successful rehabilitation. At the time of this writing, the patient continues to require a wheelchair and lives at a long-term skilled nursing facility with regular outpatient follow-up.

As mentioned previously, stroke mimics represent a sizable portion of stroke workups. Our case highlights the potential economic burden to both the medical system and the patient, as a repeated stroke workup was pursued due the patient's persistent neurologic findings in the setting of a limited differential diagnosis. This patient received over 40 imaging studies within the span of 6 months and 5 hospitalizations, in addition to numerous laboratory tests and panels. Though limited stroke mimics were initially considered on the differential, stroke was more prominently considered due to patient's seemingly acute presentation and imaging findings with infarcts corresponding to a specific vascular region. This case also highlights the importance of a continuously evolving differential diagnosis—as our patient's neurological symptoms progressed, it was key to expand the differential and integrate dermatologic findings, in the setting of neck mass on CTA

neck. The diagnosis of KLHL 11 PNS is difficult, with symptoms presenting months before most malignancies are identified. Though PNS is not a common cause of stroke-like symptoms, it should be considered in cases where stroke diagnosis is not definitive.

Conclusion

Neurologic PNS, such as KLHL 11 PNS, are being increasingly recognized as notable causes of stroke mimic. Treatment and prognosis of neurologic PNS vary significantly from stroke, therefore it is critical for medical teams in the primary care specialties as well as neurologic and oncologic consulting services to be aware of this presentation. Diagnoses such as KLHL 11 PNS highlight the necessity of interdisciplinary treatment and collaboration when establishing a differential diagnosis, as well as the importance of remaining up to date on newly discovered etiologies for stroke-like symptoms. As molecular and immunologic testing advances, and as more unusual cases provide increased awareness of overlap in presenting symptoms and subsequent radiographic findings between neurologic PNS and stroke, patient outcomes may improve due to quicker time to diagnosis. Ultimately, healthcare provider awareness of PNS syndromes—including KLHL 11 PNS—will lead to earlier diagnosis, better prognostication, lower healthcare costs, appropriate treatment, realistic expectations regarding recovery, and earlier discussions regarding goals of care.

Acknowledgments

We gratefully acknowledge Daniel Murphy, MD, and Ulrich Rassner, MD from the University of Utah Health Department of Radiology, who helped obtain and interpret imaging described above. We also gratefully acknowledge Lori Healey, MD, from the University of Utah Health Department of Pathology, who helped obtain and interpret histological slides described above.

Disclosures and Conflicts of Interest

The authors have none to declare.

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