Paraneoplastic Acute Axonal Polyneuropathy Associated with CASPR2 and LGI1 Antibodies

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Introduction

Autoantibodies to voltage-gated potassium channel (VGKC) and its associated proteins including leucine-rich glioma-inactivated 1(LGI1) and contactin-associated protein-like 2 (CASPR2) have been implicated in numerous disorders of the central and peripheral nervous systems and observed in patients with cancer.[1] While LGI1 antibodies are associated with limbic encephalitis and faciobrachial dystonic seizures, antibodies against CASPR2 result in a broad spectrum of clinical syndromes, most notably Morvan's syndrome and neuromyotonia.[1] Additionally, one study noted a 44% prevalence of underlying cancer (one-third being thymoma) in patients with both antibodies.[1]

GBS associated with CASPR2 antibodies has been reported in two pediatric cases, one with concomitant LGI1 antibody positivity.[2] We report a case of an adult patient with acute axonal sensorimotor polyneuropathy who ultimately was found to have CASPR2 and LGI1 antibodies, as well as radiographic findings suspicious for renal cell carcinoma.

Case Presentation

A 67-year-old man without preceding illness presented with a two-week history of intractable lumbar radicular pain with associated progressive, bilateral upper and lower extremity dysesthesias and weakness, requiring assistance with ambulation and feeding. His review of systems was otherwise non-contributory including an absence of constitutional symptoms. Except for a five-day history of constipation presumed secondary to narcotics recently prescribed for his new neuropathic pain, autonomic symptoms were absent. His examination was significant for normal bulk, diminished tone, and diffuse fasciculations. Upper extremity strength by Medical Research Council scale was 3/5 in bilateral shoulder abduction, elbow flexion, and elbow extension; 2/5 in bilateral wrist flexion, wrist extension, finger extension, finger abduction, and thumb abduction; and 1/5 in bilateral grip strength. Lower extremity strength was 3/5 in bilateral hip flexion, hip abduction, and knee flexion; 2/5 in bilateral knee extension, ankle dorsiflexion, ankle plantarflexion, and great toe extension. Finally, generalized areflexia was noted, as well as length-dependent hypoesthesia to all modalities with normalization around the level of the thighs and elbows.

Results

The cerebrospinal fluid analysis revealed five nucleated cells and an elevated protein (126 mg/dL; reference range: <60 mg/dL), confirming cytoalbuminologic dissociation. CSF IgG synthesis rate was increased (12.52 mg/24 h; reference range: ≤8 mg/24 h), while CSF IgG index, oligoclonal bands, and an infectious workup were normal or negative.

Electrodiagnostic studies showed findings suggestive of acute axonal sensorimotor polyneuropathy suggested by reduced compound motor action potential amplitudes (CMAPs) and multiple non-recordable sensory responses (albeit with normal superficial radial sensory conduction) (Table 1). Needle EMG was significant for reduced motor unit potential recruitment and the presence of fibrillations/positive sharp waves without motor unit remodeling (Table 2). Peripheral nerve hyperexcitability (PNH) was supported by the presence of diffuse simple fasciculations and the appearance of afterdischarges in multiple CMAPs, which obscure the F-waves (Figure 1). Additional findings included conduction slowing in the common entrapment sites including the right median and ulnar neuropathies at the wrist and elbow, respectively.

Overall, the clinical presentation of ascending numbness, proximal and distal weakness, generalized areflexia, and severe neuropathic pain, accompanied by cytoalbuminologic dissociation and the electrodiagnostic findings led us to the initial diagnosis of acute motor and sensory axonal neuropathy variant of GBS, though PNH findings were atypical.

MR scan of the entire spine was unremarkable except for an incidental finding of a left upper pole renal mass. This finding was confirmed on MR scan of the abdomen with contrast, which showed a mass 4.2 cm in greatest dimension most consistent with renal cell carcinoma (RCC), clear cell subtype (Figure 2A, 2B). Features supportive of clear cell subtype included contrast enhancement and a central area of high signal intensity on T2-weighted images with nonenhancement after contrast administration (Figure 2A, 2B).[3] This prompted a serum paraneoplastic panel (Mayo Clinic, Rochester, Minnesota, USA), which revealed positive CASPR2 and LGI1 antibodies. The remaining diagnostic studies including a complete metabolic panel and whole-body CT scans were either normal or negative, except for moderate hyponatremia.

Table 1. Nerve conduction study results.

MOTOR				
Nerve	**Onset Latency (msec)**	**Amplitude (mV-motor)**	**Conduction velocity (m/sec)**	**F-wave latency (msec)**
Right median (abductor pollicis brevis)	11.09 (wrist) (normal <4.2)	1.6 (wrist) 1.2 (elbow) (normal >5.0)	43 (normal >51)	No response
Right ulnar (abductor digiti minimi)	3.59 (wrist) (normal <4.0)	6.3 (wrist) 5.2 (below elbow) 5.0 (above elbow) (normal >5.0)	56 (below elbow) 33 (above elbow) (normal >51)	No response
Right peroneal (extensor digitorum brevis)	5.05 (ankle) (normal <5.5)	3.8 (ankle) 2.7 (fib head) 2.3 (pop fossa) (normal >2.5)	41 (fib head) 42 (pop fossa) (normal >40)	64.1 (normal <56.0)
Right tibial (abductor hallucis)	5.52 (ankle) (normal <5.6)	1.2 (ankle) 0.5 (pop fossa) (normal >2.5)	43 (pop fossa) (normal >40)	No response
SENSORY				
Nerve	**Peak Latency (msec)**	**Amplitude (µV-sensory)**	**Conduction velocity (msec)**	
Right median, ulnar, sural, superficial peroneal	No response	No response	No response	
Right radial	2.14 (normal <2.5)	19.9 (normal >15)	60	

Table 2. Electromyography results.

Muscle	**Fibrillations**	**Positive Sharp Waves**	**Fasciculations**	**Polyphasia**	**Amplitude**	**Duration**	**Recruitment**
Right tibialis anterior	1+	None	1+	Normal	Normal	Normal	Reduced
Right gastrocnemius	None	None	1+	Normal	Normal	Normal	Reduced
Right vastus lateralis	1+	1+	None	Normal	Normal	Normal	Reduced
Right tensor fasciae latae	1+	None	None	Normal	Normal	Normal	Reduced
Right biceps brachii	None	None	None	Normal	Normal	Normal	Normal
Right deltoid	1+	1+	1+	Normal	Normal	Normal	Reduced
Right triceps brachii	1+	1+	2+	Normal	Normal	Normal	Reduced
Right first dorsal interosseous	1+	None	1+	Normal	Normal	Normal	Reduced

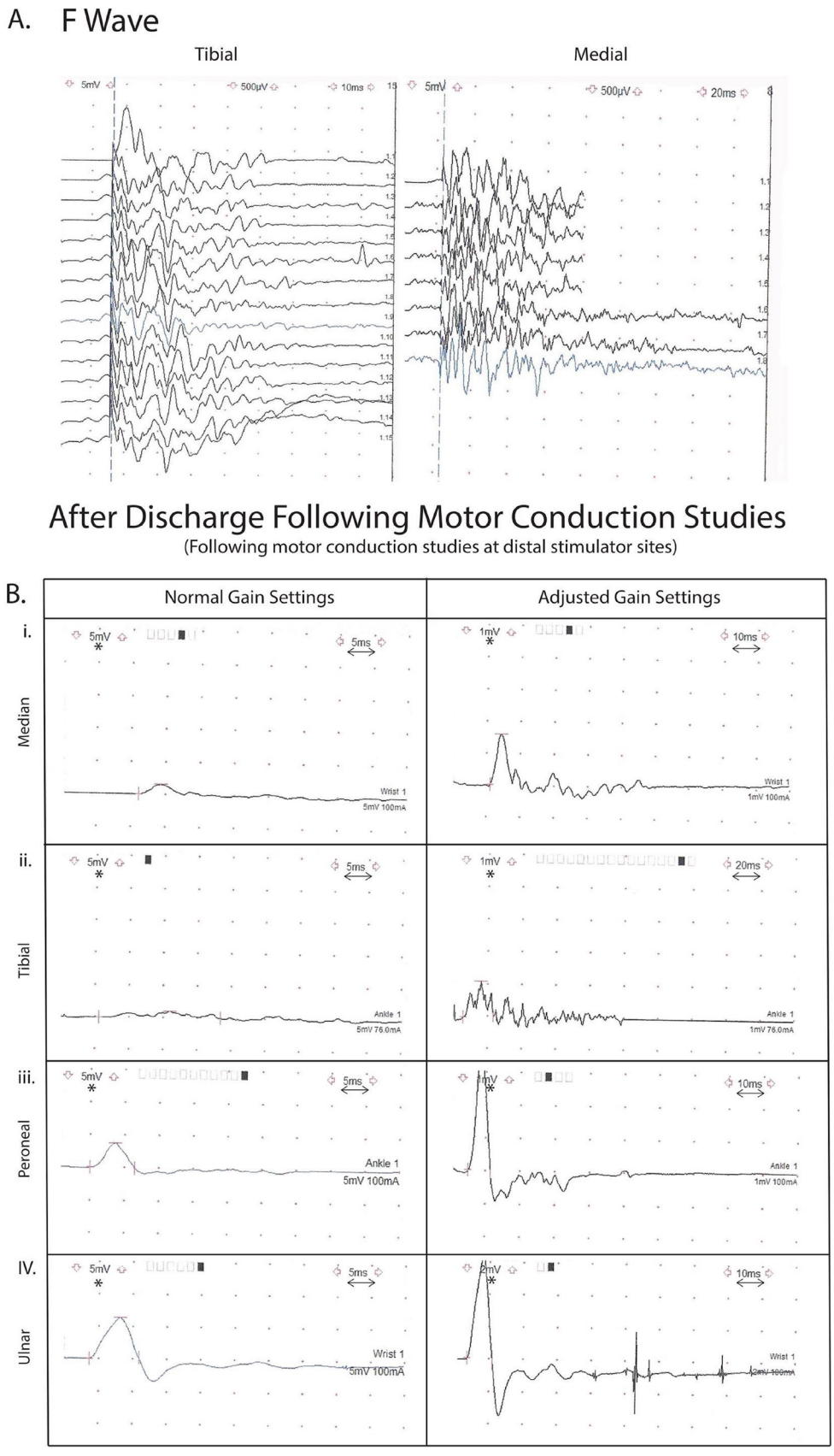

Figure 1. F-wave responses obscured by the prolonged afterdischarges (A). Prolonged afterdischarges on motor conduction studies were better visualized following adjustment of gain settings; * sensitivity , ↔ sweep speed (B).

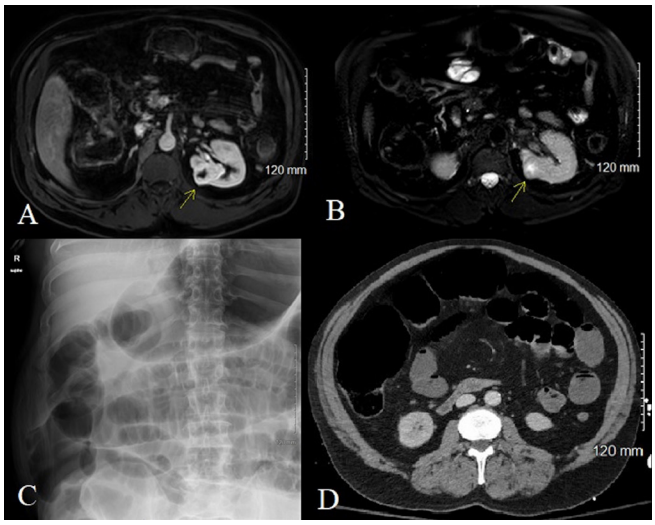

Figure 2. MR scan of abdomen, axial plane, demonstrating a 4.2 x 2.4 x 2.8 cm left upper pole exophytic contrast-enhancing renal mass (A) with central T2 hyperintensity (B) concerning for renal cell neoplasm, possibly clear cell subtype. Abdominal X-ray demonstrating distended stomach and air-filled loops of small and large bowel (C), CT scan of abdomen demonstrating diffusely distended colon (D).

Course

By hospital day three following a third of five planned total doses of intravenous immunoglobulin (IVIg) therapy at a daily dose of 0.4 g/kg, the patient had an objective improvement in strength and return of some upper extremity reflexes. Upper extremity strength was 4/5 in bilateral shoulder abduction, elbow flexion, and elbow extension; 3/5 in finger abduction; and 3/5 in bilateral grip strength. Lower extremity strength was 3/5 in bilateral hip flexion, knee flexion, and knee extension; and 2/5 in bilateral ankle dorsiflexion and ankle plantarflexion.

The patient's constipation remained refractory to conservative measures including laxatives, suppositories, and cessation of opioids. Unfortunately, on hospital day seven, the patient developed unremitting vomiting due to paralytic ileus (Figure 2C, 2D). Clinical deterioration with the development of abdominal compartment syndrome (intra-abdominal pressure of 38 mmHg) subsequently led to hemodynamic compromise and multiorgan failure, as evidenced by elevated troponin, liver function tests, and anuric renal failure. Despite continued aggressive supportive care and assistance from critical care and surgical consultants, the patient progressed into pulseless electrical activity and expired shortly thereafter. The family declined an autopsy.

Discussion

This patient's presentation of progressive limb weakness, ascending numbness, generalized areflexia, and severe neuropathic pain, coupled with a CSF cytoalbuminologic dissociation and the electrodiagnostic findings, is consistent with an acute axonal sensorimotor polyneuropathy. Additionally, the findings of a presumed RCC, elevated CSF IgG synthesis rate, and the presence of CASPR2 and LGI1 antibodies were highly suspicious for an underlying paraneoplastic basis of his polyneuropathy. Our report highlights multiple evolving concepts related to the diagnostic and prognostic value of CASPR2 and LGI1 antibodies as potential biomarkers of autoimmune neuropathies.

Pathogenesis and IVIg Responsiveness

Rare presentations of GBS associated with nodal and paranodal antibodies, including our patient's, have shown IVIg responsiveness.[2,4,5] In contrast, chronic inflammatory demyelinating polyneuropathy (CIDP) associated with nodal and paranodal antibodies including CASPR2 responds poorly to IVIg but responds to rituximab and plasmapheresis. CIDP usually is associated with IgG4 subtypes while GBS patients have IgG1 or IgG3 subtypes.[4,5] The difference in therapeutic response could therefore be explained based on Ig isotype.

Potential mechanisms for IgG1/3-mediated diseases, which are responsive to IVIg, include clustering and internalization of receptors followed by lysosomal degradation, complement-mediated membrane receptor disruption, and direct blockade of receptors.[4,5] In contrast, IgG4 acts only by disrupting the function of the target or the interaction between the target and partner protein without the ability to fix complement or crosslink antibodies (Figure 3D). IgG4 titers decline sharply with rituximab, supporting its effectiveness in IgG4-mediated disorders such as CIDP associated with nodal and paranodal antibodies.[4]

The lack of access to paranodal antibody IgG subtyping (IgG1/3 vs IgG4) and titers at our reference laboratory as well as the inability to observe our patient's longitudinal course **and pursue autopsy**, prevent us from drawing final conclusions regarding his therapeutic response to IVIg. However, when available, testing for IgG subclasses may be useful in patients with autoantibodies against paranodal proteins and their significance should be addressed in prospective studies.

Peripheral Nerve Hyperexcitability

In addition to findings suggestive of acute axonal sensorimotor polyneuropathy, the patient's electrodiagnostic testing also **suggested** PNH, as evidenced by diffuse generalized fasciculations and afterdischarges. These findings **may be** explained by the effect of antibodies to the VGKC complex, including CASPR2 and LGI1, which

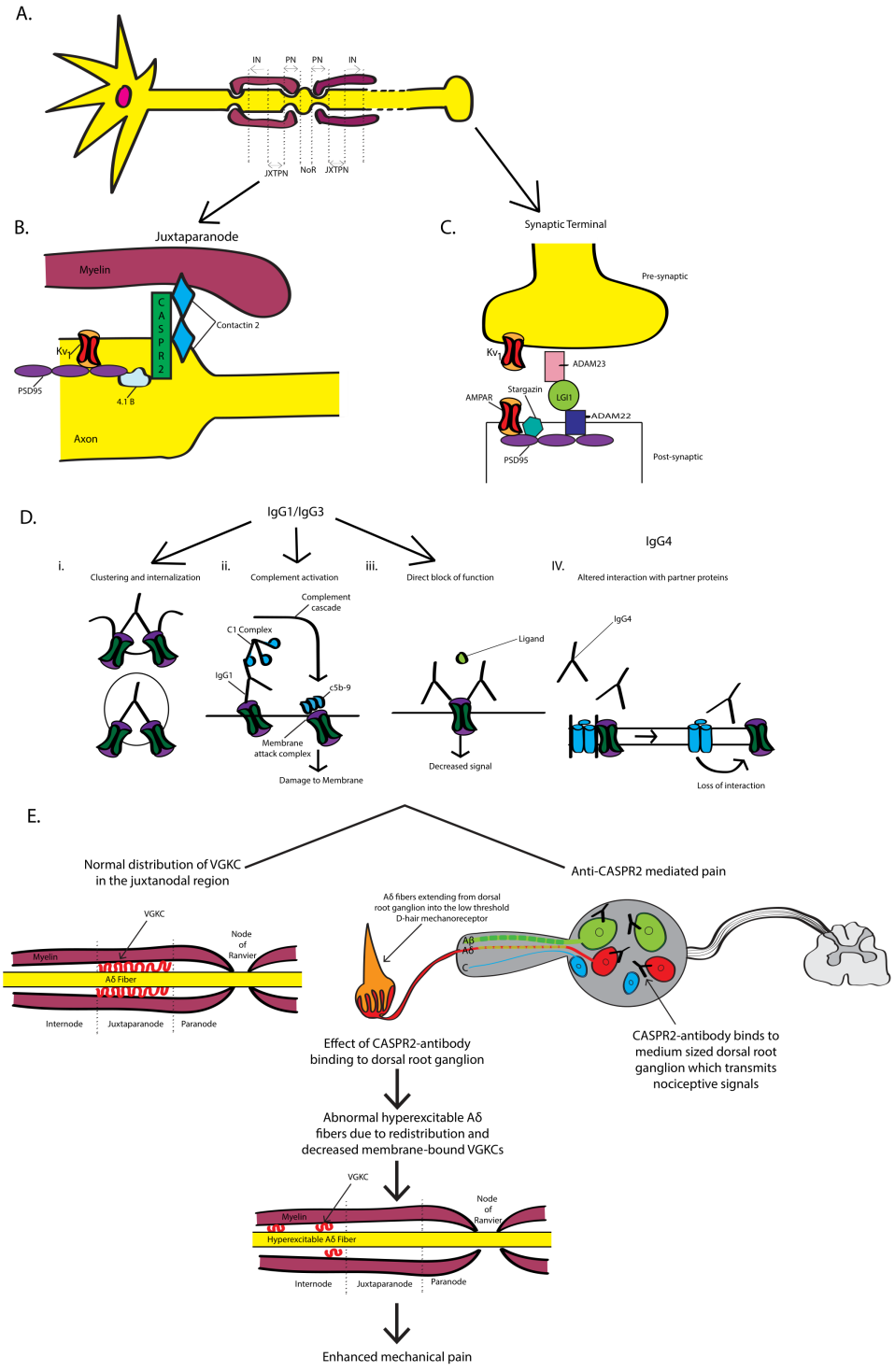

Figure 3: Schematic representation of CASPR2 and LGI1 localization at the juxta-paranode and synaptic cleft and their association with the voltage-gated potassium channel (A, B, and C). CASPR2 is a transmembrane protein which through its interaction with contactin-2 and other proteins, is responsible for the clustering of potassium channels (Kv1.1 and Kv1.2) at the juxta-paranodal region of the myelinated axons (A). Thus, CASPR2 maintains the axo-glial junction and through collaboration with Kv1 receptors, plays a prominent role in nerve repolarization. CASPR2 also prevents repetitive firing and hyperexcitability by maintaining internodal resting potential (B). LGI1 forms a trans-synaptic protein complex with pre-synaptic ADAM23, which is essential for localization of Kv1.1 and Kv1.2 subunits of VGKC, and post-synaptic ADAM22, which interacts with the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR). These interactions account for fast excitatory synaptic transmission (C).[1,4] Main pathogenic mechanisms of IgG1 and IgG3 antibodies vs IgG4 antibody (D).[4] The suggested mechanism of action of CASPR2 antibody-mediated pain (E).[10]

prevent the repolarization and termination of the neuronal action potential via a decrease in the number of functioning VGKCs and impaired voltage-gated outward potassium current (Figure 3A-3C).[1,4,5] The impulse generator in previous cases of PNH has been demonstrated to be either from the terminal arborizations of motor nerves, proximal portions of the motor nerve, or even the motoneuron, thus **potentially** explaining the presence of diffuse fasciculations in our case.[6]

Afterdischarges are defined as repetitive late potentials following initial compound muscle action potential after a stimulus. Due to the higher gain settings (100-200 μV/division), afterdischarges may be initially noted during F wave recording, however prolonged afterdischarges might obscure the appearance of F waves, as in our case (Figure 1A). As such, following the adjustment of gain settings, afterdischarges can be better visualized during motor nerve conduction studies (NCS) (Figure 1B). In one study, the sensitivity of motor NCS in spotting PNH was superior to clinical symptoms and needle EMG.[7]

In our case, with the exception of diffuse fasciculations and afterdischarges, no overt neuromyotonia or central nervous system involvement was identified to confirm previously described CASPR2/LGI1-associated Morvan's syndrome. This could be explained partly by the degree of PNH. During states of relatively low PNH, abnormal spontaneous discharges such as neuromyotonia might not be evident on resting needle EMG. However, induction of membrane hyperexcitability following electrical stimulation for motor NCS facilitates the sustained appearance of afterdischarges.[7] Moreover, a patient presenting with a syndrome consistent with GBS who developed LGI1-positive Morvan's syndrome late in their disease course has previously been described in the literature.[8] Unfortunately, our patient died soon after initial responsiveness to IVIg, which precluded the ability to observe his final clinical course.

Severe Neuropathic Pain

Our case also **was consistent with** a previous finding of severe CASPR2 antibody-associated neuropathic pain. This phenomenon is mediated by the binding of CASPR2 antibodies to the soma of medium-sized dorsal root ganglion neurons resulting in decreased membrane-bound VGKC clustering, as well as their redistribution along internal segments, leading to lower thresholds for mechanical pain and hyperexcitable Aδ fibers (Figure 3E).[9] Additional evidence for a functional rather than structural effect of antibody mediated pain was provided by rapid relief of pain after treatment as well as a normal intraepidermal nerve fiber density in previously described cases of painful inflammatory neuropathy with autoantibodies against another paranodal target, contactin-associated protein 1.[10]

Dysautonomia

The dysautonomia observed in GBS may manifest in the bowel as ileus. Additionally, features of dysautonomia independent of GBS have been described in 84% of patients with both CASPR2 and LGI1 antibodies.[1] Previous studies have demonstrated the presence of VGKCs in enteric neurons at every level of the gut. These findings provide pathological relevance to the severity of gastrointestinal neuromuscular dysmotility with anti-VGKC antibodies found in our case.[11] Gastrointestinal dysautonomia in our patient was evidenced by paralytic ileus, with abdominal imaging showing distended small and large bowel without obvious obstruction (Figure 2C, 2D). Persistent ileus ultimately contributed to the development of rising intrabdominal pressures and fatal abdominal compartment syndrome.[12]

Abdominal compartment syndrome is characterized by sustained intra-abdominal pressure in excess of 20 mmHg (most often measured indirectly via an intravesical catheter at end expiration in the supine position) in combination with new-onset organ dysfunction.[12] Common risk factors include intra-abdominal masses, bowel obstruction, aggressive fluid resuscitation, intraperitoneal bleeding, and third-space fluid shifts from conditions that increase capillary permeability. Abdominal compartment syndrome has been described in cases of severe ileus, similar to our patient.[12] An additional contributor to our patient's fulminant ileus was use of opioid pain medications, however ileus persisted even after these were discontinued, suggesting dysautonomia was at least in part contributing. Our case highlights the importance of recognizing the potentially fatal complication of abdominal compartment syndrome arising from dysautonomia. In similar clinical scenarios, early utilization of intravesical pressure measurement and consultation with critical care and surgical consultants may be useful.

Paraneoplastic Basis

Lastly, the radiographic finding suspicious for RCC was of unproven clinical significance. **Although anywhere from 10-40% of patients with RCC are noted to have paraneoplastic syndromes, they are most often endocrine or neuroendocrine in nature. In one review of paraneoplastic syndromes associated with RCC including almost 300 journal articles, paraneoplastic syndromes with neurologic manifestations were only identified in 22 cases. Among these, a spectrum of neurological paraneoplastic syndromes were reported and include motor neuron disease, demyelinating polyneuropathies, and myopathies.[13] Identification**

of paraneoplastic antibodies has been limited in these cases with the exception of a single case of GAD antibody positive paraneoplastic stiff person syndrome in a patient with RCC.[14] It therefore remains unknown whether or not the neurologic syndromes observed in these patients were immune-mediated or whether the antibodies simply have not yet been identified. Although CASPR2 and LGI1 antibodies are not considered typical paraneoplastic antibodies, they have been described infrequently in solid organ tumors, and are posited to have mediated GBS in this patient with suspected RCC.[15] Screening for underlying malignancy in patients presenting with otherwise unexplained GBS may, therefore, be fruitful.

In summary, **recognizing its limitations,** the present case adds to a growing body of literature describing CASPR2/LGI1 as a biologically plausible autoimmune target in the pathogenesis of a GBS-like syndrome, but with multiple unique features including PNH, severe neuropathic pain, dysautonomia, IVIg responsiveness, and a possible association with RCC.

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