Jahnke S, Atiya M, Kurzen JL. Rapidly Progressive Bilateral Leg Weakness in a 65-Year-Old Man: A Case Report. *hb TIMES Schw Aerztej*. 2025;16(1):28-31.
doi:10.36000/hbT.2025.16.003

CASE REPORT

Rapidly Progressive Bilateral Leg Weakness in a 65-Year-Old Man: A Case Report

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Keywords: paraneoplastic neurological syndromes, polyneuroradiculopathy, adenocarcinoma, leg weakness

https://doi.org/10.36000/hbT.2025.16.003

healthbook TIMES Das Schweizer Ärztejournal Journal Des Médecins Suisses

Vol. 16, Issue 1, 2025

Paraneoplastic neurological syndromes can affect any part of the nervous system, often have a stereotypical presentation, occur in association with a tumor, and have an antibody-mediated pathogenesis.
We describe the case of a 65-year-old previously healthy crane operator who presented to the emergency department due to symmetrical, gradually progressive gait instability and leg weakness. Due to evidence of a pulmonary mass in combination with polyneuroradiculopathy, a thoracoscopic upper lobe resection was performed with histological findings of an adenocarcinoma. Postoperatively, there was a marked improvement in gait and distal paraparesis. Despite an extensive search, no paraneoplastic autoantibodies could be detected in our patient. According to the 2021 consensus criteria, both the clinical phenotype and the presence of a tumor, as well as the determination of anti-neuronal antibodies in serum and cerebrospinal fluid, are essential for diagnosis. This enables a diagnosis to be made in four categories (definite, probable, possible, non-paraneoplastic neurological syndrome [PNS]).

PEER REVIEWED ARTICLE

Peer Reviewers:
Prof. Dr Uwe Schlegel, Klinik für Neurologie Hirslanden, Zurich, und Neurozentrum Bellevue, Zurich
One anonymous peer reviewer

Received on January 25, 2025; accepted after peer review on February 27, 2025; published on March 17, 2025.

Introduction

Paraneoplastic neurological syndromes (PNS) are immunological reactions to tumor antigens that can affect any part of the nervous system and often precede tumor diagnosis. PNS can be defined as remote effects of

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malignancies with immune-mediated pathogenesis[1,2] that are not caused by the tumor itself, its metastases, infection, ischemia or metabolic derailments.[1, 3] They can involve all areas of the central and peripheral nervous system, the neuromuscular endplate and muscle. Affected patients have an unfavorable prognosis.

According to the new consensus guidelines with the diagnostic criteria for PNS from 2021,[4] the certainty of diagnosis is divided into four categories according to the PNS Care Score (definite, probable, possible, non-PNS) based on the initial clinical presentation, the presence of antibodies, and a tumor diagnosis.[4] As they often precede tumor diagnosis, the search for tumors can be significantly influenced by detecting certain antibodies that indicate the tumor entity and location. However, a negative antibody finding does not rule out a PNS, as among part of the cases, no paraneoplastic antibodies are detectable.[5] Furthermore, the diagnostic value of paraneoplastic antibodies depends on how they are tested.[6]

We aim to highlight and discuss the clinical presentation, diagnostic approach, and therapeutic management based on a case of paraneoplastic neurological syndrome associated with the initial diagnosis of bronchus carcinoma treated at our hospital.

Case Presentation

Patient information and personal history

A 65-year-old obese man, working as a crane operator presents to the emergency department due to unsteady gait and symmetric leg weakness that has occurred symmetrically and gradually over the past 2 months and has increased rapidly over the past 3 weeks (**Figure 1**).

The patient has noticed increasing weakness in his legs; he has recently had difficulty getting out of bed in the morning, which is why he has seen his general practitioner. In addition to the loss of strength, he noticed an unsteady gait (see **Video 1** in the Supplementary Files, which shows the unsteady, broad-based gait). The patient does not remember any trauma, and a possible viral infection with some fatigue and subfebrile temperatures had been present 3–4 weeks before the appointment. Secondary diagnoses are diabetes mellitus, an intranasal malignancy (treated with radiotherapy more than 10 years ago), and a cigarette consumption of 40 pack years.

Clinical examination

GAIT ANALYSIS

The patient presents as an obese 65-year-old man with BP 144/76 mmHg, P 72/min, SpO_2 93% on room air, and cardiopulmonary findings were unremarkable. There was no tenderness to pressure over the spine. The

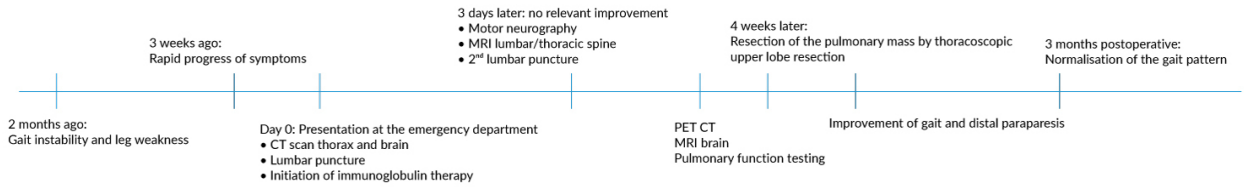

Figure 1. Timeline of the patient's symptoms, diagnostic steps and treatment milestones.

The course of events is illustrated from the onset of gait instability to post-operative recovery (time axis not linear). CT, computed tomography; MRI, magnetic resonance imagine; PET, positron emission tomography.

muscle reflexes were uniformly lively except for weakened Achilles tendon reflexes bilaterally. There was paresis of foot/toe/big toe elevation (strength grade 3–4 according to Janda [0–5]), foot drop (strength grade 4), foot supination (strength grade 4), pronation (strength grade 3–4), knee flexion (strength grade 4+) and hip abduction (strength grade 4–5) on the right side. The gait pattern was slightly unsteady, with reduced heel walk and toe walk and a positive Trendelenburg sign on both sides (reduced heel walk in **Video 2** and toe walk in **Video 3**, respectively). The Romberg test showed a slight unsteadiness, but the sensibility test is unremarkable for all qualities. Bladder and bowel function were unremarkable.

DIAGNOSTIC ASSESSMENT

To clarify further the cause of the patient's complaints, a computed tomography (CT) scan of the spine was performed directly in the emergency department showing slight degenerative changes in the thoracic axial skeleton with lumbar disc protrusion and possible irritation of the right L4 nerve root. No spinal canal stenosis was found, and a 2.5 cm pulmonary mass of in the apical right upper lobe segment was described as a secondary finding. A CT scan of the skull was unremarkable.

As the CT scan findings do not explain the weakness in both legs, a lumbar puncture of the cerebrospinal fluid (CSF) was performed in the emergency department, revealing an albumin level only slightly above normal with a normal cell count (**Table 1**).

So, based on the suspected cytoalbuminous dissociation, a possible Guillain-Barré syndrome (GBS) or another demyelinating condition was suspected.

Immunoglobulin therapy (40 g/day) was started over the weekend (as the patient presented on a Friday evening). After three days of treatment, the patient reported no significant change in his condition.

The findings from the motor neurography, conducted more than four weeks after the onset of symptoms, reveal reduced compound muscle action potentials in arm and leg nerves, normal distal motor latency, and a normal nerve conduction velocity. Together with the absence of cytoalbuminous dissociation, these results cast doubt on the diagnosis of GBS. The most

Table 1. Cerebrospinal fluid (CSF) on day 1, 8, 28 and 63 (postoperative).

Cerebrospinal fluid (CSF)	Standard value	Day 1	Day 8	Day 28	Day 63 post-op
Color	Clear	Clear	Clear	Clear	Clear
Total cell count	<5/µl	3	36	18	0
Polynuclear cell count	<5/µl	2	10	0	0
Mononuclear cell count	<5/µl	1	26	18	4
Glucose	2.3–3.9 mmol/L	4.7	4.6	5.1	4.6
Protein	0.15–0.45 g/L	0.56	0.57	0.78	0.63

notable abnormalities are a delay in the tibial nerve F-waves to 70 ms and pathological spontaneous activity in the L4/5 myotome. These findings suggest proximal demyelination, potentially indicative of a partial conduction block, while the spontaneous activity observed in the EMG points to axonal damage.

Next, a contrast-enhanced magnetic resonance imaging (MRI) examination of the spine (thoracic and lumbar spine) was performed, the main finding being a long-distance fine enhancement of individual nerve fibres of the cauda equina on both sides. The subsequent repeat lumbar puncture showed a pleocytosis of 26 cells, and the albumin level remained stable.

Furthermore, the pulmonary mass in the area of the right upper lobe was clarified on an outpatient basis using positron emission tomography (PET)-CT, which showed a high degree of metabolic activity, suggesting possible bronchus carcinoma (**Figure 2**). Supplementary examinations, including MRI of the skull and pulmonary function tests, did not reveal any relevant new findings.

The simultaneous presence of a possible bronchus carcinoma and the progressive, unexplained bilateral leg weakness suggested a possible diagnosis of paraneoplastic syndrome. Therefore, paraneoplastic antibodies were determined in serum and cerebrospinal fluid (**Table 2**) according to the updated diagnostic criteria for paraneoplastic neurologic syndromes.[4]

Serologically, only ganglioside antibodies were borderline positive in the first determination; these were negative in the control. Thus, no specific paraneoplastic antibodies could be detected.

A diagnosis of polyradiculoneuropathy was made based on the presence of rapidly progressive, painless, distal paraparesis of the legs, electrophysiologically acute denervation in EMG, reduced compound muscle action potential (cMAP), delayed F-waves and contrast enhancement of the lumbar nerve roots, as well as an increased cell count and a slight protein elevation in the cerebrospinal fluid.

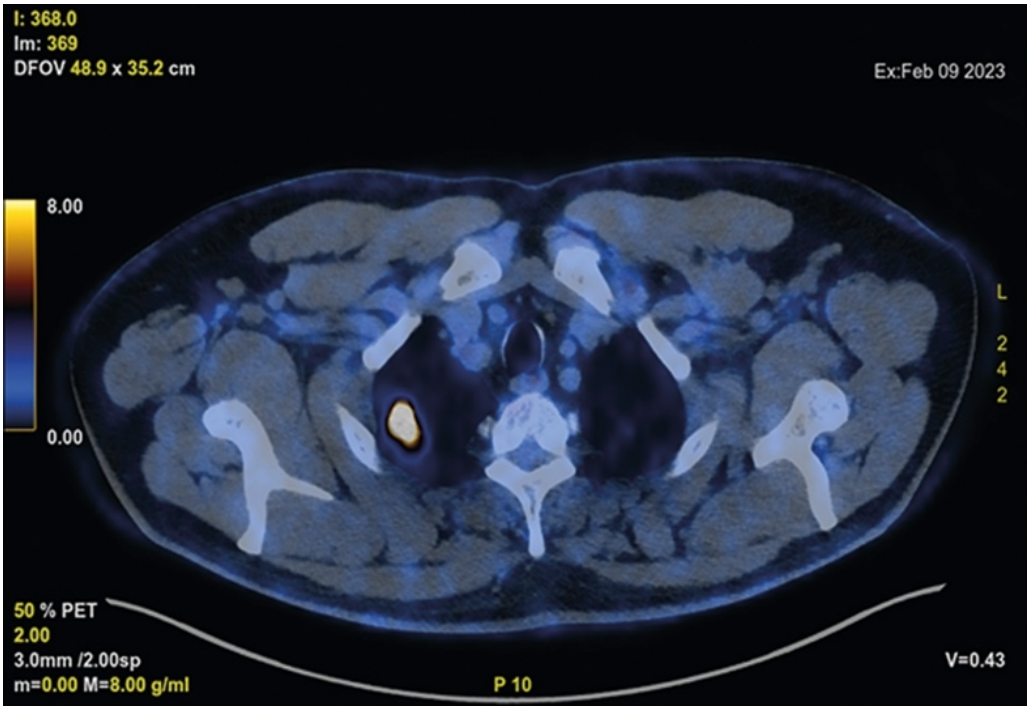

Figure 2. Positron emission tomography (PET)-computed tomography (CT) with highly active pulmonary nodulus in the right apical upper lobe.

No metabolically active lymph nodes or metastases were detectable.

Table 2. Paraneoplastic antibodies in serum and cerebrospinal fluid.

Paraneoplastic antibodies	Serum	Cerebrospinal fluid
Anti-Hu (ANNA-1)	-	-
Yo (PCA-1)	-	-
Ri (ANNA-2)	-	-
ANNA-3	-	-
Amphiphysin	-	-
CRMP5/CV2	-	
K-Channel CASPR2	-	-
K-Channel LGI1	-	-
Ca-Channel NType	-	-
Ca-Channel PQTyp	-	-
AMPAR	-	-
NMDAR	-	-
DPPX	-	-
GABABR	-	-
Ganglioside	(+)/-	
NIF	-	-
Acetylcholine receptor	-	
MuSK-Ab, Titin	-	

ANNA, Antineuronal nuclear antibody; PCA-1, Anti-Purkinje cell antibody; CRMP5, Collapsin response-mediator protein 5; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR, N-methyl-D-aspartate receptor; DPPX, Dipeptidyl-peptidase-like-protein-6; GABABR, Gamma-aminobutyric acid B receptor; NIF, Neuronal intermediate filament; CASPR2, Anti-contactin-associated protein-like 2; MuSK-Ab, Muscle-specific kinase antibody; Ri (ANNA-2), anti-neuron-specific cell nuclear antibodies-2; Yo (PCA-1), Purkinje-cell antibodies-1.

SURGERY AND HISTOPATHOLOGY

Four weeks after the initial presentation to the emergency department, the pulmonary mass was removed by thoracoscopic upper lobe resection; histological examination revealed an adenocarcinoma. Shortly after surgery, there was a marked improvement in gait and distal paraparesis (improved normal gait pattern visible in **Video 4**, with improved heel walk visible in **Video 5** and toe walk in **Video 5**, respectively). Three months post-operatively, the gait pattern was largely normalised (**Video 7**), with heel walking (**Video 8**) and toe walking (**Video 9**) now possible.

Discussion

PNS are immunological reactions to tumor antigens that can affect any part of the nervous system and often precede tumor diagnosis.[4] According to an epidemiological study, the incidence is 4.4/100,000, suggesting underdiagnosis.[3,7] In the case of cancer patients, it is estimated that approximately one in 300 patients is affected.[3,8] The more frequent use of immune checkpoint inhibitors in oncological practice is expected to lead to an increased frequency of similar syndromes, as the alteration of the immune system leads to neurological immunological syndromes as a side effect, ranging from myasthenic syndromes to neuropathies.[9,10]

PNS occur in a variety of tumors: They are most common in small cell lung cancer (SCLC), ovarian cancer, and breast cancer. PNS are less common in non-small cell lung cancer (NSCLC), lymphoma, thymoma/thymic carcinoma, and testicular and prostate cancer.

A set of recommended diagnostic criteria for PNS was first established by a panel of international experts in 2004.[11]

In 2021, another expert panel proposed an update to the diagnostic criteria. It replaced the term “classic” with “high-risk” phenotypes and non-classic with “intermediate-risk” phenotypes, which had previously been used in the guidelines.[4] The antibodies previously described as onco-neuronal are now classified as high risk (>70% associated with carcinoma), medium risk (30–70% associated with carcinoma), and low risk (<30% associated with carcinoma) paraneoplastic antibodies. In addition to the clinical phenotype, the presence or absence of a tumor and the determination of neuronal antibodies in serum and CSF are essential for the diagnosis according to the 2021 consensus criteria using the PNS-Care Score. This allows a diagnosis to be made in four categories (definite, probable, possible, non-paraneoplastic neurological syndrome [PNS]).[4]

Despite an extensive search, no paraneoplastic autoantibodies could be detected in our patient (**Table 2**). According to the 2015 German Society for Neurology (DGN) guidelines, based on the 2004 consensus criteria,[11] the diagnosis of a PNS could still be definitively made if no antibodies

were detected. However, according to the updated consensus guidelines of 2021,[4] we can at best speak of a probable diagnosis: it is an intermediate-risk phenotype on the clinical level, resulting in 2 points; no anti-neuronal antibodies were detected on the laboratory level, resulting in 0 points, and cancer consistent with phenotype was found, resulting in 4 points. This adds up to 6 points, indicating a probable PNS, even if the clinical course is strongly in favour of the diagnosis.

Differential diagnoses included a paraneoplastic or diabetic[12] etiology of the polyradiculoneuropathy. However, the pain typically associated with diabetic lumbar polyradiculoneuropathy (DLRN) was absent. Painless manifestations of diabetic polyradiculoneuropathy are rare and usually present with sensory involvement, without an elevated cell count in the cerebrospinal fluid, and tend to regress only slowly. Infectious causes, such as Lyme disease or Lues, are also known triggers but were ruled out serologically. As the patient reported symptoms compatible with a viral infection a few weeks before the onset of symptoms, a postviral pure motor polyradiculoneuropathy is a possible differential diagnosis, while unlikely. The slightly elevated albumin level with normal cell count in CSF, initially interpreted as cytoalbuminous dissociation that lead to a suspected Guillain-Barré syndrome (GBS) or another demyelinating condition and initiation of immunoglobulin therapy, could also be explained by diabetes mellitus. The search for tumors can be significantly influenced by the detection of certain antibodies that indicate the tumor entity and location. However, a negative antibody finding does not rule out a PNS, as in a proportion of cases, no paraneoplastic antibodies are detectable.[5] Furthermore, the diagnostic value of paraneoplastic antibodies depends on how they are tested.[6] Although commercial kits that test multiple antibodies can be helpful for initial screening, the number of false-positive and -negative results is particularly high for line blots assessing Yo, Ma2, CV2/CRMP5, and SOX1 antibodies.[13-17] Therefore, reference laboratories should perform the antibody testing in patients with high suspicion for PNS but negative routine screening of antibodies in clinical or commercial laboratories.[13,14] The tumor screening in previously tumor-free patients depends on the type of neuronal antibody and should be repeated every 4–6 months for 2 years or as appropriate in the individual case if the tumor search was negative.[4]

Conclusion

The presence of PNS should be considered in the setting of subacute, rapidly progressive neurological symptoms, particularly in the case of a high-risk phenotype (e.g. Lambert-Eaton syndrome, encephalomyelitis, limbic encephalitis), signs of inflammation in the CSF (mild lymphocytic pleocytosis usually <100 cells/μL) or evidence of a barrier dysfunction on MRI. As PNS may precede a tumor diagnosis, the differential diagnosis of PNS is of great importance. The search for tumors can be significantly influenced by

paraneoplastic antibodies which indicate the entity and location. In rapidly progressive neurological syndromes with no overt explanation and red flags, such as relevant smoking or smoking history, a systematic search for an underlying tumor is warranted.

Ethics approval

Written informed consent for publication of this case report has been obtained from the patient. This applies in particular to the 9 video sequences documenting the gait before and after the operation, which are provided as supplementary material to this article.

Conflict of Interest

The authors have declared that they have no potential conflicts of interest.

Funding

The authors have declared that no financial support was received from any organization for the submitted work.

Author Contributions

Concept, JLK, SJ, MA. Writing, reviewing, editing, JLK, SJ, MA. All authors have read the submitted manuscript and are jointly responsible for all aspects of the work.

Supplementary Material: Videos

Video 1–3: Preoperative gait analysis

Videos 4–6: Shortly after surgery (postoperative)

Videos 7–9: Three months postoperatively

See links on top of this article.

Submitted: January 25, 2025 CEST. Accepted: February 27, 2025 CEST. Published: March 17, 2025 CEST.

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SUPPLEMENTARY MATERIALS

Video 1 unsteady, broad-based gate at presentation to emergency

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Video 2 reduced heel walk presentation to emergency

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Video 3 reduced toe walk presentation to emergency

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Video 4 gait pattern shortly after surgery update

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Video 5 heel walk shortly after surgery update

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Video 6 Improved toe walk shortly after surgery update

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Video 7 largely normalised gait pattern three months post operatively

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Video 8 heel walk three months post operatively

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Video 9 toe walk three months post operatively

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