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NARRATIVE REVIEW/CASE REPORT

PARANEOPLASTIC NEUROLOGICAL SYNDROMES ASSOCIATED WITH ANTI-HU ANTIBODIES IN AN OVARIAN CANCER PATIENT: A CASE REPORT AND NARRATIVE LITERATURE REVIEW

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ABSTRACT: This article focuses on ovarian cancer associated with paraneoplastic neurological syndromes (PNS) linked to anti-Hu antibodies. Starting from a rare and unusual clinical case, we review PNS from a global perspective, then focus on PNS related to ovarian cancer, especially those linked to anti-Hu antibodies, discussing the pathophysiology, diagnosis, and lastly, treatments. Specifically, the patient exhibited cerebellar ataxia and nausea concurrently with abdominal pain, leading to further investigations that revealed progressive thrombocytosis, a significant pelvic mass on imaging, and the presence of anti-Hu-D antibodies. Notably, surgical removal of a carcinosarcoma-like tumor resulted in a significant alleviation of the paraneoplastic symptoms.

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Impact statement: This work sheds light on a rare and poorly understood clinical condition: PNS associated with anti-Hu antibodies in ovarian cancer. By combining a detailed case report with a narrative review, this article provides a comprehensive overview of a condition that remains underrecognized in both clinical and research settings. The manuscript offers essential tools and insights for clinicians and researchers to better navigate the complexities of PNS, highlighting the need for heightened awareness and further investigation. By delineating the current state of knowledge and identifying gaps in our understanding, this work paves the way for more effective diagnosis, treatment, and future research endeavors, ultimately contributing to improved patient outcomes in this challenging field.

Key words: *Paraneoplastic Neurological Syndromes; anti-Hu antibodies; ovarian cancer; cerebellar ataxia; thrombocytosis; onco-rheumatology.*

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INTRODUCTION

Paraneoplastic neurological syndrome (PNS) is a group of neurological disorders arising from an abnormal immune response to the nervous system triggered by a distant tumor (1, 2). The term "paraneoplastic", derived from the Greek words "para" (beside), "neo" (new), and "plasis" (formation) (3), signifies that the neurological symptoms in cancer patients are not caused by the direct invasion of the tumor or metastasis. Instead, these symptoms result from the production of autoantibodies, cytokines, hormones, or peptides that affect various organ systems. This immune response occurs because the immune system targets neoplastic cells, recognizing them as foreign elements. Symptoms of PNS can vary widely, as the autoantibodies produced may affect any part of the nervous system, from central to peripheral regions.

Initially, the incidence of PNS was estimated to be rare, affecting less than 0.01% of cancer patients overall (4, 5). However, more recent studies indicate that clinically disabling PNS may occur more frequently, with incidence rates ranging from 0.5% to 1% among all cancer patients (6). Similarly, data on paraneoplastic syndromes in ovarian cancer are not well-defined. Early reports suggested that symptomatic paraneoplastic disorders were rare in ovarian cancer patients, with an incidence of approximately 1 per 1000 new cases (7). Recent studies, however, suggest a stronger association.

Diagnosing PNS can be challenging, but addressing it is crucial for several reasons: it can be an early indicator of cancer or reveal undetectable cancer, it can be debilitating and requires proper management, and it serves as a prognostic factor for cancer (8-12).

The antibodies implicated in PNS related to ovarian cancer include anti-Hu antibodies (8), anti-Yo antibodies, and anti-NMDA receptor antibodies (9, 12). The ovarian cancer histotypes that can cause PNS include teratoma (13), serous ovarian carcinoma (11), and borderline ovarian mucinous tumor (14). However, only a few cases of PNS specifically associated with anti-Hu antibodies have been reported in ovarian cancer patients.

Given the complexity and heterogeneity of the subject, this paper follows a deductive structure. It begins with a general review of PNS, then focuses on PNS in relation to ovarian cancer, specifically anti-Hu related PNS, and finally presents a clinical case of PNS associated with anti-Hu antibodies in a patient with carcinosarcoma-like neoplasia of the ovary.

NARRATIVE REVIEW

The methodology of the narrative review is reported in **Supplementary Document 1**, "Narrative Review Methodology". Since there are no commonly validated guidelines for narrative reviews, we adhered to the PRISMA guidelines as detailed in **Supplementary Document 2**, "PRISMA Guideline", and **Supplementary Figure 1**, "PRISMA Flowchart."

Classification of PNSs based on area involved

PNSs is characterized by a wide array of clinical manifestations since any part of the nervous system can be involved. In **Table 1** we provide a narrative of the various types of PNSs, their clinical presentations, associated antibodies, and the cancers with which they are commonly associated (15-22). They are classified according to which part of nervous system is involved.

Central nervous system involvement

Limbic encephalitis is one of the most studied forms of central nervous system involvement in PNS. Patients typically present with memory loss, confusion, seizures, and psychiatric symptoms. The antibodies most frequently associated with limbic encephalitis include anti-NMDA receptor, anti-GABAb receptor, anti-Hu, anti-Ma2, and anti-AMPAR. This syndrome is often linked to small cell lung cancer (SCLC), testicular cancer, ovarian teratoma, and thymoma. Another significant central nervous system manifestation is paraneoplastic cerebellar degeneration, characterized by ataxia, dysarthria, and nystagmus. The antibodies anti-Yo, anti-Hu, anti-Tr, and anti-Ri are commonly involved, and this condition is primarily associated with breast cancer, ovarian cancer, and Hodgkin lymphoma. The clinical course can be rapid, leading to profound disability if not promptly recognized and treated. Brainstem encephalitis, which presents with cranial nerve palsies, ataxia, and dysphagia, is another clinical form. Anti-Hu and anti-Ma2 antibodies are typically implicated, with SCLC and testicular cancer being the most common associated malignancies. Opsoclonus-myoclonus syndrome is characterized by rapid, involuntary eye movements and myoclonus, often accompanied by ataxia. This rare syndrome

Table 1. *Classification of paraneoplastic neurological syndromes.*

LOCATION TYPE	SYNDROMES	SYMPTOMS	ANTIBODIES	CANCER ASSOCIATION
CNS	Limbic encephalitis	Memory loss, confusion, seizures, psychiatric symptoms	Anti-Hu, Anti-Ma2, Anti-NMDA receptor, Anti-GABAb receptor, Anti-AMPAR	SCLC, testicular cancer, ovarian teratoma, thymoma
CNS	Paraneoplastic cerebellar degeneration	Ataxia, dysarthria, nystagmus	Anti-Yo, Anti-Hu, Anti-Tr, Anti-Ri	Breast cancer, ovarian cancer, Hodgkin lymphoma
CNS	Brainstem encephalitis	Cranial nerve palsies, ataxia, dysphagia	Anti-Hu, Anti-Ma2	SCLC, testicular cancer
CNS	Opsoclonus-myoclonus syndrome	Rapid eye movements, myoclonus, ataxia	Anti-Ri	Neuroblastoma (children), breast cancer (adults)
CNS	Encephalomyelitis	Diffuse inflammation of the brain and spinal cord	Anti-Hu, Anti-Ma2	SCLC, testicular cancer
PNS	Dorsal root ganglionopathy	Sensory ataxia, numbness, pain	Anti-Hu	SCLC
PNS	Motor neuronopathy	Muscle weakness, atrophy, fasciculations	Anti-Hu	SCLC
PNS	Autonomic neuropathy	Orthostatic hypotension, gastrointestinal dysmotility, urinary dysfunction	Anti-Hu	SCLC
PNS	Neuromyotonia (Isaacs' syndrome)	Muscle stiffness, cramps, fasciculations	Anti-Caspr2	Thymoma
NJD	Lambert-Eaton myasthenic syndrome	Proximal muscle weakness, autonomic dysfunction	Anti-P/Q-type voltage-gated calcium channel	SCLC
NJD	Myasthenia gravis	Muscle weakness, ptosis, diplopia	Anti-acetylcholine receptor, Anti-MuSK	Thymoma
Myelopathies	Paraneoplastic myelopathy	Spasticity, weakness, sensory loss	Anti-Hu, Anti-CRMP5	SCLC
CAR	Cancer-associated retinopathy	Photopsia, vision loss	Anti-recoverin, Anti-enolase	SCLC, melanoma
CAR	Melanoma-associated retinopathy	Night blindness, vision loss	Anti-Tr	Melanoma

CNS: Central Nervous System involvement; PNS: Peripheral Nervous System involvement; NJD: Neuromuscular Junction Disorder; CAR: Cancer-Associated Retinopathy.

is associated with anti-Ri antibodies and is seen in children with neuroblastoma and adults with breast cancer. Encephalomyelitis involves diffuse inflammation of the brain and spinal cord. Anti-Hu and anti-Ma2 antibodies are commonly detected in affected individuals, who often have SCLC or testicular cancer. The broad symptomatology can mimic other inflammatory and infectious conditions, complicating the diagnostic process.

Peripheral nervous system involvement

Sensory neuronopathy, also known as dorsal root ganglionopathy, presents with sensory ataxia, numbness, and pain. Anti-Hu antibodies are typically involved, and SCLC is the most commonly associated cancer. Motor neuronopathy is characterized by muscle weakness, atrophy, and fasciculations, with anti-Hu antibodies again playing a central role. This condition is predominantly seen in patients with SCLC. The clinical presentation can mimic amyotrophic lateral sclerosis, making differentiation crucial for appropriate management. Autonomic neuropathy manifests with orthostatic hypotension, gastrointestinal dysmotility, and urinary dysfunction. Anti-Hu and anti-NMDA receptor antibodies are commonly detected, and SCLC is fre-

quently the underlying cancer. Neuromyotonia, or Isaacs' syndrome, presents with muscle stiffness, cramps, and fasciculations. This rare condition is associated with anti-Caspr2 antibodies and is typically linked to thymoma. The muscle hyperactivity can lead to significant discomfort and functional impairment. All these conditions could lead to progressive sensory loss severely impairing function and necessitating early intervention to manage symptoms and address the underlying malignancy.

Neuromuscular junction disorders

Lambert-Eaton Myasthenic Syndrome (LEMS) is characterized by proximal muscle weakness and autonomic dysfunction. It is associated with anti-P/Q-type voltage-gated calcium channel antibodies and is commonly seen in patients with SCLC. The presentation can be similar to myasthenia gravis, but the involvement of autonomic symptoms and the characteristic electrophysiological findings help in differentiation. Myasthenia gravis presents with muscle weakness, ptosis, and diplopia. It is associated with anti-acetylcholine receptor and anti-MuSK antibodies and is typically linked to thymoma. The fluctuating nature of muscle weakness and the response to acetylcholinesterase inhibitors are key diagnostic clues.

Myelopathies

Paraneoplastic myelopathy is characterized by spasticity, weakness, and sensory loss. Anti-Hu and anti-CRMP5 antibodies are often detected, and SCLC is the most common associated malignancy. The presentation can resemble other causes of myelopathy, necessitating a thorough evaluation to identify the paraneoplastic nature.

Cancer-associated retinopathy

Cancer-associated retinopathy (CAR) typically presents with photopsia and vision loss and is commonly associated with anti-recoverin and anti-enolase antibodies. It is often linked to SCLC but can occur with various cancers. Notably, melanoma causes a distinct form of CAR with a different pathogenesis. In this case, patients experience not only vision loss but also night blindness, with anti-Tr antibodies being commonly associated.

Comprehensive classification of paraneoplastic antibodies and pathogenetic mechanisms

Autoantibodies related to PNSs are the main pathogenic factors. In **Table 2**, we categorize these antibodies based on their target antigens: intracellular antigens and neuronal surface antigens (NSAbs). This classification highlights differences in pathogenic mechanisms and clinical implications. Anti-intracellular antigen antibodies typically indicate cytotoxic T-cell-mediated neuronal injury, whereas NSAbs are directly pathogenic and often respond well to immunotherapy. **Table 2** also includes the cancer risk associated with each antibody, with higher risk indicating a stronger likelihood of cancer association.

Anti-intracellular antigen antibodies

Anti-intracellular antigen antibodies target intracellular neuronal proteins, leading cytotoxic T-cell-mediated neuronal injury.

Among these, high-risk antibodies are strongly associated with cancer. For instance, Anti-Hu (ANNA-1) antibodies target Hu proteins (HuD, HuC, Hel-N1). They affect the nervous system by causing encephalomyelitis, sensory neuronopathy, and autonomic dysfunction. Another high-risk antibody, Anti-Yo, targets Purkinje cell cytoplasmic proteins (CDR2, CDR2L) and is linked to ovarian and breast cancer. It primarily causes paraneoplastic cerebellar degeneration. Similarly, Anti-Ri (ANNA-2) antibodies target Nova proteins and are associated with breast and gynecological cancers. These antibodies lead to opsoclonus-myoclonus syndrome by causing T-cell-mediated neuronal injury in the brainstem and cerebellum, leading to involuntary eye movements and myoclonus. Anti-Ma/Ta antibodies, for example, target Ma proteins, leading to limbic encephalitis and brainstem encephalitis. They are linked to testicular cancer (15).

Lower-risk antibodies, such as Anti-GAD, target glutamic acid decarboxylase and are associated with various cancers, often in conjunction with diabetes. They can cause stiff-person syndrome and cerebellar ataxia by disrupting inhibitory neurotransmission (15).

Neuronal surface antibodies (NSAbs)

NSAbs target neuronal cell surface proteins and are directly pathogenic, often responding well to immunotherapy.

Intermediate-risk antibodies include Anti-NMDA receptor antibodies and are associated with ovarian teratomas. They cause psychiatric symptoms, seizures, and dyskinesias by binding to NMDA receptors (NR1 subunit) leading to receptor internalization and dysfunction, which disrupts synaptic transmission (15). Anti-AMPAR antibodies belongs

Table 2. *Comprehensive classification of paraneoplastic antibodies.*

RISK LEVEL	ANTIBODY	MECHANISM	CANCER ASSOCIATION
	ANTI-INTRACELLULAR ANTIGEN ANTIBODIES		
High	Anti-Hu (ANNA-1)	Cytotoxic T cells recognize and destroy neurons expressing Hu proteins, leading to widespread neuronal death and inflammation	Small cell lung cancer (SCLC)
High	Anti-Yo	T cells target Purkinje cells, causing their death and leading to cerebellar degeneration and ataxia	Ovarian cancer and breast cancer
High	Anti-Ri (ANNA-2)	T-cell-mediated neuronal injury in the brainstem and cerebellum, leading to involuntary eye movements and myoclonus	Breast and gynecological cancers
High	Anti-Ma/Ta	Cytotoxic T cells attack neurons expressing Ma proteins, causing inflammation and neuronal loss in the limbic system and brainstem	Testicular cancer
Low	Anti-GAD	Autoimmune response targets GAD-expressing neurons, disrupting inhibitory neurotransmission and causing muscle stiffness and ataxia	Various cancers, often associated with diabetes
	NEURAL SURFACE ANTIBODIES (NSABS)		
Intermediate	Anti-NMDA Receptor	Antibodies bind to NMDA receptors, causing receptor internalization and dysfunction, leading to disrupted synaptic transmission and neuropsychiatric symptoms	Ovarian teratoma
Intermediate	Anti-AMPAR	Antibodies bind to AMPA receptors, altering receptor function and causing excitotoxicity and inflammation in the limbic system	Various malignancies
Intermediate	Anti-GABAb	Antibodies inhibit GABAb receptor function, reducing inhibitory neurotransmission and leading to limbic system hyperexcitability and inflammation	Small cell lung cancer (SCLC)
Low	Anti-LGI1	Antibodies disrupt the VGKC complex, leading to altered neuronal excitability and inflammation in the limbic system	Thymoma and other malignancies
Low	Anti-metabotropic glutamate receptor (mGluR1 and mGluR5)	Antibodies alter mGluR function, disrupting glutamate signaling and causing neuronal dysfunction and inflammation	Hodgkin lymphoma
Low	Anti-Caspr2	Antibodies disrupt VGKC complex function, causing hyperexcitability of peripheral and central neurons, leading to neuromyotonia and autonomic dysfunction	Thymoma
	OTHER RELEVANT ANTIBODIES		
High	Anti-SOX1	T cells target neurons expressing SOX1, leading to neuronal loss and dysfunction	Small cell lung cancer (SCLC), Lambert-Eaton myasthenic syndrome (LEMS), paraneoplastic cerebellar degeneration (PCD)
Intermediate	Anti-P/Q-type Voltage-Gated Calcium Channel (VGCC)	Antibodies inhibit VGCC function at the neuromuscular junction, reducing acetylcholine release and causing muscle weakness	Small cell lung cancer (SCLC), Lambert-Eaton myasthenic syndrome (LEMS)

Antibody high, intermediate, low risk levels are indicated in green, cerulean, light cerulean respectively.

to Intermediate-risk class. They target the AMPA receptor (GluR1/2 subunits) and are linked to various malignancies. These antibodies cause limbic encephalitis by altering receptor function and causing excitotoxicity and inflammation in the limbic system (15). Anti-GABAb antibodies target the GABAb receptor and cause limbic encephalitis by inhibiting GABAb receptor function, reducing inhibitory neurotransmission and leading to limbic system hyperexcitability and inflammation (16).

Lower-risk antibodies, such as Anti-LGI1 antibodies, associated with thymoma and other malignancies, target the leucine-rich glioma-inactivated 1 protein, causing limbic encephalitis and faciobrachial dystonic seizures (16). Anti-metabotropic glutamate receptor (mGluR1 and mGluR5) antibodies target these receptors and are associated with Hodgkin lymphoma. They cause various neurological symptoms, including ataxia, by disrupting glutamate signaling and causing neuronal dysfunction and inflammation (16). Anti-Caspr2 antibodies, target the contactin-associated protein-like 2 and are associated with thymoma. They cause Morvan syndrome leading to hyperexcitability of peripheral and central neurons, resulting in neuromyotonia and autonomic dysfunction (15).

Other relevant antibodies include Anti-SOX1 (High-Risk), which targets the SOX1 protein and is associated with SCLC, LEMS, and paraneoplastic cerebellar degeneration (PCD) (18). Additionally, Anti-P/Q-type Voltage-Gated Calcium Channel (VGCC) antibodies (High-Risk) target the P/Q-type VGCC and are associated with SCLC. They cause LEMS by inhibiting VGCC function at the neuromuscular junction, reducing acetylcholine release and causing muscle weakness (18).

Diagnosis

Diagnosing PNS involves ruling out other, more common causes of neurological symptoms. These alternative diagnoses include infections, autoimmune diseases not related to cancer, tumors, neurodegenerative disorders, and toxic or metabolic issues.

PNS diagnosis is based on the PNS-Care Score, which takes into account the type of neurological symptoms (that needs to be addressed as high-risk or intermediate phenotype or phenotype not associated to cancer), the presence of specific neuronal antibodies (that needs to be classified according to the association-risk to cancer), and whether there is a clear diagnosis of cancer. The diagnosis of PNS is, then stratified into three levels of certainty: possible, probable, and definite. Regarding phenotype scoring, Encephalomyelitis, Limbic encephalitis, rapidly progressive cerebellar syndrome, Opsoclonus-myoclonus, Sensory neuronopathy, Gastrointestinal pseudo-obstruction (enteric neuropathy) and Lambert-Eaton myasthenic syndrome are consider high risk while intermediate-risk phenotypes are those characterized by rapidly progressive development (<3 months) or by inflammatory findings in the Cerebrospinal fluid (CSF) or brain/spine at MRI evaluation. Some of the followings are examples of this category: Encephalitis other than well-defined LE, anti-NMDAR encephalitis, Brainstem encephalitis, Morvan syndrome, Isolated myelopathy, Stiff-person syndrome, and Paraneoplastic polyradiculoneuropathies. Clinical focus for diagnosis is reported in **Supplementary Document 3** (23).

Treatments

The management of PNS involves, as a primary goal, whenever possible, the treatment of the underlying malignancy since surgical removal of the tumor can significantly resolve PNS symptoms. Additionally, standard cancer treatments such as chemotherapy and radiation are essential to control the malignancy, which can subsequently reduce the immune response against neuronal tissues (24). Immunosuppressive therapies are indicated in support of oncological treatment or whenever primary disease is not yet identified. Immunosuppressive therapy commonly includes high-dose corticosteroids such as methylprednisolone to reduce inflammation and immune response (25). Intravenous immunoglobulins (IVIG) are administered to modulate the immune system and reduce the activity of autoantibodies (26). In cases where initial treatments are ineffective, rituximab, an anti-CD20 monoclonal antibody, is used to deplete B cells (27). Plasmapheresis is used in severe cases to quickly reduce antibody levels (28). For PNSs associated with antibodies targeting intracellular mechanisms, treatment generally begins with high-dose corticosteroids, such as methylprednisolone and if there is no response, cyclophosphamide can be considered. However, increasing immunosuppression should be avoided to prevent exacerbating the oncological condition. Experimental treatments are also being explored. The use of natalizumab, a monoclonal antibody targeting alpha-4 integrin, is being explored in a

phase II trial showing that while some patients experienced stabilization or mild improvement, the overall efficacy was not superior to existing treatments (29).

PNS and ovarian cancer

It is crucial to thoroughly consider neurological symptoms in ovarian cancer patients in clinical practice and research. Advances in diagnostics and broader dissemination of medical literature reveal that paraneoplastic disorders in gynecological cancers are more common than previously thought. Giometto *et al*. (30) found that 10.5% of 899 PNS patients had ovarian cancer. Similarly, Hill *et al*. (31) reported a standardized incidence ratio of 10.5 for women developing dermatomyositis before being diagnosed with ovarian cancer. Teratoma (13), serous ovarian carcinoma (11), and borderline ovarian mucinous tumor (14) are the ovarian cancer histotypes most commonly associated with PNS. Below, we review the onconeural antibodies most frequently associated: anti-NMDAR antibodies, anti-Yo antibodies, and anti-Hu antibodies.

Anti-NMethyl-D-Aspartate Receptor (NMDAR) antibody

Anti-NMDAR antibodies are primarily involved in paraneoplastic encephalitis, the most common PNS associated with ovarian tumors that are ovarian teratomas (up to 65% of cases) (32). NMDARs facilitate calcium influx upon activation, triggering intracellular signaling pathways that modify synaptic strength and structure, thereby supporting synaptic plasticity (33). That is why they are crucial in neurodevelopment. Disruptions in these processes can lead to neurological disorders such as autism and schizophrenia (34). Furthermore, NMDARs play a significant role in adult neurogenesis and the normal development of the dentate gyrus by influencing the survival and proliferation of neural progenitor cells (35). NMDARs are also essential for learning and memory since they mediate long-term potentiation (LTP) and long-term depression (LTD) (36).

Anti-Yo antibodies

Anti-Yo antibodies are usually associated with PCD. They have been found in 23% of cases of ovarian malignant tumors, half of which manifesting clinical signs of PCD (9). These antibodies by targeting cerebellar degeneration-related proteins (CDR2 and CDR2L) expressed by Purkinje cells and tumor cells lead an autoimmune attack involving both cellular and humoral immune mechanisms. Additionally, the genetic alteration of Yo antigens in tumor cells can trigger immune tolerance breakdown, further driving the autoimmune process (36, 38, 39).

Anti-Hu antibodies

Anti-Hu antibodies are most often associated with SCLC; however, they are also reported in association with 2.5% of gynecological cancers (40). Typical manifestations are paraneoplastic encephalitis, brainstem pathology, cerebellar disorder, and sensory neuropathy (41) and the most frequent ovarian tumors associated are malignant carcinomas such as, high-grade serous carcinoma (8), borderline ovarian mucinous tumor (14) and ovarian dysgerminoma (42) as showed in **Table 3.**

Hu proteins, also known as ELAVL4, are typically present in the central and peripheral nervous systems but can be aberrantly expressed in ovarian cancers. This aberrant expression disrupts immune tolerance, leading to an immune attack against neurons where the production of Anti-Hu antibodies represents an essential step because they lead the immune attack mediated by cytotoxic T lymphocytes (CTLs). This result in neuronal death and inflammation. This process is evidenced by the presence of CD8+ T cells and microglial activation in affected neural tissues (26, 27). Neurological disorders depend on the affected neuronal populations, and they include sensory neuronopathy, encephalomyelitis, and other forms of neuronal degeneration (26, 43). The underlying mechanisms of this immune response were also demonstrated in experimental models where CTLs from mice immunized with HuD peptide induced neuronal cell death in culture (27).

Anti-Hu antibodies were first identified in patients with comorbid subacute sensory neuropathy and SCLC (25). Subsequent studies confirmed that while anti-Hu antibodies can be observed in patients with various extra thoracic cancers such as prostate, breast, gastrointestinal, bladder, and ovarian cancers, they remain highly specific for lung cancer, particularly SCLC (25, 45). Neurological disorders due to anti-Hu antibody differ widely since they go from limbic encephalitis to brainstem encephalitis, chronic gastrointestinal pseudo-obstruction, and cerebellar degeneration. Patients frequently experience severe sensory deficits, ataxia, autonomic dysfunction, and cognitive impairments. The involvement of both central and peripheral nervous systems is common,

Table 3. *Summary of Case Reports on anti-Hu antibodies related PNS in ovarian tumors.*

CASE REPORT	CLINICAL MANIFESTATION	TYPE OF TUMOR	ABS DETECTION METHOD
Graus *et al.* (42)	Encephalomyelitis	Dysgerminoma	Detected by IHC
Graus *et al.* (42)	Encephalomyelitis	Not reported	Detected by IHC
Kalanie *et al.* (2014)	Trigeminal neuralgia - Limbic encephalitis	Intestinal-type mucinous borderline tumor	Detected in serum
Yoshida *et al.* (2019)	Aphasia - encephalopathy	High-grade serous carcinoma	Detected in CSF

IHC: Immunohistochemistry; CSF: Cerebrospinal Fluid.

and the severity of symptoms often correlates with high disability and poor prognosis (26, 43). Diagnosis of anti-Hu antibody associated PNS in ovarian cancer patients follows the consensus criteria for the diagnosis of PNS by Graus *et al*., that were later updated in 2021 (23). The detection of anti-Hu antibodies in serum and CSF using immunohistochemistry, western blot, or cell-based assays is crucial for confirming the diagnosis (26, 44).

Regarding ovarian cancer, only few cases of PNS associated with anti-Hu antibodies have been reported as detailed in **Table 3.** Hiroshi Yoshida *et al*. (8) reported a case of a 68-year-old woman who was diagnosed with a high-grade serous carcinoma associated with associated anti-Hu-mediated encephalopathy. Hossein Kalanie *et al*. (14) described a case of a 76-year-old female patient with trigeminal neuralgia as the first clinical manifestation of a borderline ovarian mucinous tumor caused by anti-Hu antibodies. Lastly, Francesc Graus *et al*. (21) reviewed 200 patients with paraneoplastic encephalomyelitis (PEM) caused by anti-Hu antibodies, and among these, one case of dysgerminoma associated with such antibodies has been reported. Here, we report a case of anti-Hu antibody mediated PNS in a patient affected by advanced carcinosarcoma-like neoplasia of the ovary. The patient had clinical diagnosed PNS during the course of the oncologic disease and had regression of symptoms after surgery.

CASE REPORT

A 39-year-old female patient presented in 2023 to our Emergency Department of G. Martino University Hospital in Messina, with hyperpyrexia and pelvic pain, associated with a discernible pelvic mass. She was aware of a suspected abdominal mass, having undergone ultrasound, CT, and MRI scans a few weeks prior; however, the results of these scans were not accessible at the time of presentation. She had previously been tested for tumor markers, revealing a significantly elevated CA-125 level of 1163 U/ml. The patient was nulliparous, with a BMI of 26, and had no significant medical history except for insulin resistance. Her family history was notable for breast cancer. Upon initial examination, the patient appeared cooperative and well-oriented, with vital parameters within the normal range except for an elevated temperature of 38.5 °C. She presented with pallor and signs of dehydration. While her urine output was normal, she reported constipation and had experienced a significant decrease in appetite over the past week and nausea, though without any episodes of vomiting. Notably, her mobility was compromised; she exhibited a scything gait, characterized by dragging her right leg and displaying overall poor coordination. Her ECOG (Eastern Cooperative Oncology Group) Performance Status was scored at 2. The abdominal examination revealed a globular abdomen with asymmetric morphology due to the pelvic mass, which extended approximately 5 cm above the transverse umbilical line. The abdomen was soft and non-tender upon superficial palpation, with mild pain upon deeper palpation in the lower quadrants, where increased firmness was noted. The gynecological examination indicated normal external genitalia and vagina, a norm conformed cylindrical cervix, and an enlarged, irregularly shaped, and mildly tender uterus. A hard, mildly tender, and poorly mobile mass was palpable in the left iliac fossa and Douglas' pouch. There was no genital bleeding. After physical examination the conducted laboratory results showed anemia (Hb 9.6 g/dL) associated to low iron levels (3.6

mmol/L), leukocytosis (WBC 18,000/mm^2), thrombocytosis (PLT 674,000/mm^2), elevated C-reactive protein (20.10 mg/dL), and increased LDH levels (1639 U/L) while the rapid cultures for aerobic and anaerobic bacteria, as well as fungi, were negative. Given the comprehensive clinical presentation, which included abdominal pain, hyperpyrexia, signs of malnutrition and dehydration, constipation, nausea, ataxia, a suspect abdominal mass, anemia, and a potential infection, the decision was made to admit the patient to our ward. Initial treatment comprised antibiotics, antipyretic agents and low molecular weight heparin to address the acute symptoms and underlying conditions. To further investigate the abdominal mass and assess its characteristics, we ordered a chest X-ray and a contrast-enhanced CT scan of the abdomen and pelvis, as the patient refused to undergo an ultrasound pelvic examination for her abdominal pain. Chest X-ray and contrast-enhanced CT, revealed a modest right pleural effusion and a thickening of fibrotic nature near the costal-phrenic gap while abdominal and pelvic CT scans displayed a heterogeneous solid mass with colliquative components, measuring approximately 22 cm in diameter, significantly occupying the lower hemiabdomen and displacing the uterus anteriorly (Supplementary Document 4). The ovaries appeared compressed, with a cystic formation approximately 4 cm in diameter on the left ovary. A significant adenopathy packet was present in a para-aortic location, and a heterogeneous solid mass approximately 7 cm in diameter was noted in the left adrenal lodge. Minimal peri-hepatic and peri splenic ascitic effusion was also observed. While the abdominal pain, hyperpyrexia, signs of malnutrition and dehydration, and constipation could be attributed to the presence of a 22 cm heterogeneous solid mass with colliquative components occupying the lower hemiabdomen, the accompanying anemia and suspected infection may suggest the malignant nature of the mass and initial occlusion. However, the nausea without vomiting, the excessively high thrombocytosis, which exceeds typical inflammatory responses, and particularly the ataxia-like clinical presentation are not commonly associated with direct symptoms of a malignant abdominal and pelvic mass. Given these observations, the clinical symptoms appeared more consistent with a paraneoplastic syndrome. Pursuing this hypothesis, we conducted serum tests for a panel of antibodies including anti-Hu, anti-Yo, anti-Ri, anti-Ma, anti-NMDA, anti-AMPAR, anti-GABAb, anti-LGI1, and anti-metabotropic glutamate receptor antibodies. Of these, only anti-Hu tested positive. During the first week of hospitalization, the patient required parenteral intravenous nutrition due to persistent nausea and worsening signs of constipation, alongside ongoing intravenous antibiotic therapy and low molecular weight heparin. Despite these interventions, her clinical conditions, including nausea, ataxia, abdominal pain, and constipation, deteriorated, as did her laboratory values. After approximately 10 days of hospitalization, laboratory tests showed hemoglobin levels at 8.6 g/dL, white blood cells at 21,700/mm^2, and an increase in platelets to 1,085,000/mm^3. Consequently, following a multidisciplinary evaluation, the patient was scheduled for surgical intervention under general anesthesia for diagnostic, staging, and therapeutic purposes. The surgery began with a diagnostic laparoscopy, revealing a voluminous left adnexal mass infiltrating the anterior wall of the uterus, obliterating the Douglas' pouch, and adhering to the rectosigmoid junction posteriorly. No metastasis was observed in other abdominal organs, and with a PI score under 8, we proceeded with an operative laparotomy, and we completed a R0-debulking surgery. Histological examination of the resected neoplasia revealed a carcinosarcoma-like tumor with immunohistochemical profile as follows: CK AE1/AE3 +++, CK 8/18 ++, Vimentin ++, CK 7 -, CK 20 -, CD 34 -/+ (focal), PAX 8 -, WT 1 -, Calretinin -, HMB 45 -, S-100 -, CD 31 -, ERG -, Inibin -, Desmin -, Myogenin -, ER -, CD 99 -, CD 117 -. Ki67 > 70%. According to the FIGO (Federation Internationale de Gynecologie et d'Obstetrique) classification, the tumor was staged as III A1. Neurological examination at 10th day after surgery confirmed that the patient was alert, cooperative, and oriented in time and space. Mobility was possible with a cautious gait and a widened base of support, typical post-surgery. The examination of cerebral nerves showed no damage; muscle tone, strength, and trophism were normal across all limbs, with normally elicitable osteotendinous reflexes and normal coordination tests. Since most of the neurological symptoms regressed, no other evaluation of onconeural marker was done. By day 23 post-surgery she did not show any neurological signs or symptoms with a complete resolution after surgery. The patient was discharged in stable condition. Follow-up data are not included, as further monitoring was conducted outside of this report's scope.

DISCUSSION

Challenges in diagnosis and treatment

Managing PNS in ovarian cancer patients is challenging due to the absence of specific, well-defined protocols for diagnosis, treatment, and follow-up because of the lack of comprehensive data. To fill the gap in the literature on this topic, we first reviewed the general literature on PNS in cancer patients, then we reported our case being only the fifth documented case of PNS linked to Anti-Hu in ovarian cancer patient.

The updated diagnostic criteria by Graus *et al*. (23) are essential for improving the identification of PNS. Although our case initially showed Anti-Hu antibody positivity, it is important to note that PNS can still be diagnosed in the absence of detectable antibodies. The scoring system introduced by Graus *et al*. accommodates diverse clinical presentations and aids in recognizing PNS even when antibodies are not present. As example, a notable case reported by Muni RH involved a 28-year-old Chinese woman with a recurrent benign ovarian teratoma with bilateral horizontal gaze palsy, right facial paresis, and bilateral trigeminal hypesthesia. Tests for antineuronal antibodies (including anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-Ma1, anti-Ma2, and anti-CV2/CRMP5) were negative but MRI revealed a high signal in the rostral pons. Neurological recovery occurred within two weeks of surgical removal of the teratoma and treatment with intravenous corticosteroids and immunoglobulin (45).

Recognizing neurological disorders as part of PNSs is crucial for early cancer diagnosis. Historically, neurological symptoms were often not linked to cancer, leading to delayed diagnoses. For instance, Steven MM in 1982 reported a case where progressive cerebellar degeneration in an ovarian carcinoma patient went undiagnosed for nearly four years. Post-mortem histology revealed a complete loss of cerebellar Purkinje cells (46). Kalanie H (14) reported a case of a 76-year-old woman from Iran who presented with trigeminal neuralgia unresponsive to medication, followed by progressive neurological symptoms including somnolence, confusion, agitation, depersonalization, and visual hallucinations. Eight weeks after the initial evaluation, a large ovarian mass was identified by CT scan. The surgical removal of the 20-cm borderline mucinous tumor resulted in rapid neurological recovery, with full recovery noted at a one-year follow-up. Greenlee in 1983 further illustrated the importance of early PNS diagnosis in two cases. The first involved a 50-year-old woman who developed severe neurological symptoms, including vertigo, nausea, nystagmus, dysarthria, ataxia, and photophobia. Despite advanced diagnostic efforts, her ovarian carcinoma was diagnosed too late for surgical intervention. Postmortem examination revealed extensive metastasis and cerebellar atrophy with a complete loss of Purkinje cells. In the second case, a 58-year-old woman initially presented with dizziness, nausea, vomiting, and diplopia, which progressed to severe neurological impairment over two years. Ovarian cancer was diagnosed postmortem after it had metastasized and invaded the esophagus. Her condition rapidly deteriorated, leading to severe cachexia and eventual death. Postmortem examination revealed metastatic ovarian adenocarcinoma and cerebellar atrophy with extensive Purkinje cell loss.

Predicting the onset of clinical symptoms related to PNS in ovarian cancer patients is challenging. In our case, neurological symptoms were noted at hospital admission. However, PNS can also develop later, even after the completion of oncological treatments. Yoshida (8) reported a patient with advanced high-grade serous carcinoma. She underwent chemotherapy and extensive debulking surgery. After treatment, she developed jargon aphasia and was diagnosed with non-convulsive status epilepticus. Despite effective treatment with levetiracetam, plasma exchange, and methylprednisolone, she experienced cancer recurrence and died 14 months after surgery and 4 months after PNS onset.

In our case, the patient had a definitive diagnosis of PNS with a PNS-Care score of 10, due to a high-risk phenotype (3 points), high-risk antibody (3 points), and cancer consistent with the phenotype and antibody (4 points). Although the patient's neurological symptoms could have been overlooked due to the large abdominal mass, the PNS diagnosis significantly influenced postoperative management and counseling. The successful resolution of neurological symptoms following radical tumor excision highlights the connection between effective cancer treatment and PNS resolution. This underscores the potential value of early PNS diagnosis in improving patient outcomes. Currently, the role of antibodies linked to PNS in ovarian cancer patients as prognostic factors remains underexplored. There is insufficient data to establish these antibodies as reliable markers for predicting the onset and progression of PNS.

Revisiting historical perspectives on PNS treatment

In 1983, Hall DJ (47) reviewed paraneoplastic cerebellar degeneration in ovarian cancer patients and found that most did not benefit from tumor removal. He noted no correlation between cerebellar degeneration progression and carcinoma. These conclusions were based on limited data and less advanced diagnostics. At that time, tumors were removed at more advanced stages and in a less radical manner, allowing more time for immunological processes to generate autoimmune responses that continued to support PNS even after tumor excision. Today, improvements in cancer diagnostics and more aggressive surgeries have enhanced outcomes. For instance, in our case, the patient's neurological symptoms resolved within one-month post-surgery without the need for immunosuppressive therapy. The importance of surgical removal of ovarian tumor in solving PNS is further highlighted by other cases reported by Muni RH (45) and Kalanie H (14). Another relevant case by Nokura K. in 1997 (48) involved a 19-year-old Japanese woman who developed reversible limbic encephalitis caused by an ovarian teratoma, without detectable anti-neuronal antibodies (anti-Hu, anti-Yo). She initially presented with headache, nausea, and fever, progressing to memory loss and psychosis, ending in convulsions and coma. After unsuccessful treatments with intravenous acyclovir and high-dose corticosteroids, resection of the 8 cm pelvic mass led to significant cognitive recovery.

While historical perspectives may have indicated limited benefits from treating the malignancy, contemporary evidence suggests that effective cancer treatment, including surgical intervention, can resolve PNS symptoms without the need for additional immunosuppressive therapy. However, for patients where cancer remains undetected or they are unfit for surgery, temporary immunosuppressive therapy can manage neurological symptoms without delaying oncological treatments.

Future insights and implications

Only some ovarian cancers lead to PNS because cancer cells must express specific antigens, and the immune system must generate antibodies that cross-react with and target the nervous system. Today, we cannot predict which ovarian cancers will lead to PNS due to unknown factors such as the specific molecular features leading to antigen expression, whether these antigens can serve as markers for personalized management, and the immune system's role in PNS pathogenesis. Understanding these aspects is crucial for improving diagnosis and treatment strategies to enhance overall survival and quality of life in oncological care.

This complexity is further compounded by the use of immunotherapies in oncology, which present a significant consideration. While they enhance the immune response against cancer, they might also increase autoantibody production, raising the risk of autoimmune PNS. This dual effect necessitates careful evaluation of the benefits and risks of immune-enhancing treatments in PNS-associated ovarian cancer. Conversely, immunosuppressive treatment for PNS could exacerbate oncological disease, highlighting the need for a balanced approach (49-52).

Additionally, the integration of chemotherapy and surgery has transformed ovarian cancer into a chronic disease, often leading to multiple surgeries, relapses, and chemotherapy resistance (53). As the disease becomes more chronic, the likelihood of molecular changes increases, potentially leading to antigen expression that can induce autoimmune diseases. This rising risk of PNS in chronic ovarian cancer cases underscores the need for improved management strategies.

CONCLUSIONS

This case report underscores the complexity and rarity of PNS associated with anti-Hu antibodies in ovarian cancer patients. It highlights the need for more data to establish standardized management protocols and emphasizes the importance of early and integrated treatment approaches. Together with the literature review, we aim to contribute to a deeper understanding of the condition and underscore the necessity for continued research and collaboration for this specific group of patients characterized by oncological, neurological and rheumatological challenges.

COMPLIANCE WITH ETHICAL STANDARDS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The Authors have declared no conflict of interests.

Availability of data and materials

The original contributions presented in the study are included in the article, further inquiries can be directed to the Corresponding Author.

Authors' contributions

Conceptualization, CM, AE, AI, CP; methodology, SB, CM and FD; investigation, CN, LP, LP; resources, MRC and CM; writing-original draft preparation, CM, CCN, LP, CP; writing-review and editing, CM, FD, CCN, CP; visualization, MRC, CP, LP, SB; supervision, AE, AI; project administration, CM, CCN. All Authors have read and agreed to the published version of the manuscript.

Ethical approval

Human studies and subjects

In preparing this clinical report, we took extensive measures to protect patient privacy and confidentiality. Firstly, all personally identifiable information has been anonymized, ensuring that names, addresses, dates of birth, medical record numbers, and other identifying details have been removed. We used generic terms to replace specific details, describing patients in general terms to prevent identification. Additionally, specific dates and locations have been masked or generalized to further ensure anonymity. The data used in this report were obtained retrospectively from our database. Patient, at the time of accessing our university hospital, signed an informed consent allowing the use of their personal data for scientific purposes. Therefore, informed consent was already in place, and patients were aware of the potential use of their anonymized data in scientific research. Lastly, we adhered to the principle of minimal necessary information, including only the data that is essential for the clinical or research purpose of this report.

Animal studies

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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SUPPLEMENTARY DOCUMENT 1: NARRATIVE REVIEW METHODOLOGY

This narrative review was conducted using PubMed as the primary database to identify relevant studies. While narrative reviews lack standardized guidelines, the study selection process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for transparency and systematicity. The process is showed in the PRISMA flow diagram (**Supplement Figure 1**) and detailed below.

Initially, studies related to anti-Hu antibodies and ovarian cancer were identified using the search terms "anti-Hu AND ovarian cancer", yielding 18 articles, of which only 4 were case reports detailing clinical cases and primary research. To ensure a comprehensive review, both primary and secondary research were included using the following Medical Subject Headings (MeSH): "(neurological[Title] OR encephalit*[Title] OR cerebel*[Title]) AND (ovarian[Title] OR ovary[Title] OR adnexa[Title])" and "((paraneoplastic neurological syndrome*[Title]) AND (cancer[Title])". Given that much of the PNS data is derived from lung cancer studies, research on PNS associated with various cancer types was also included. This search strategy produced 309 results, from which 45 were selected as most relevant based on the following inclusion and exclusion criteria.

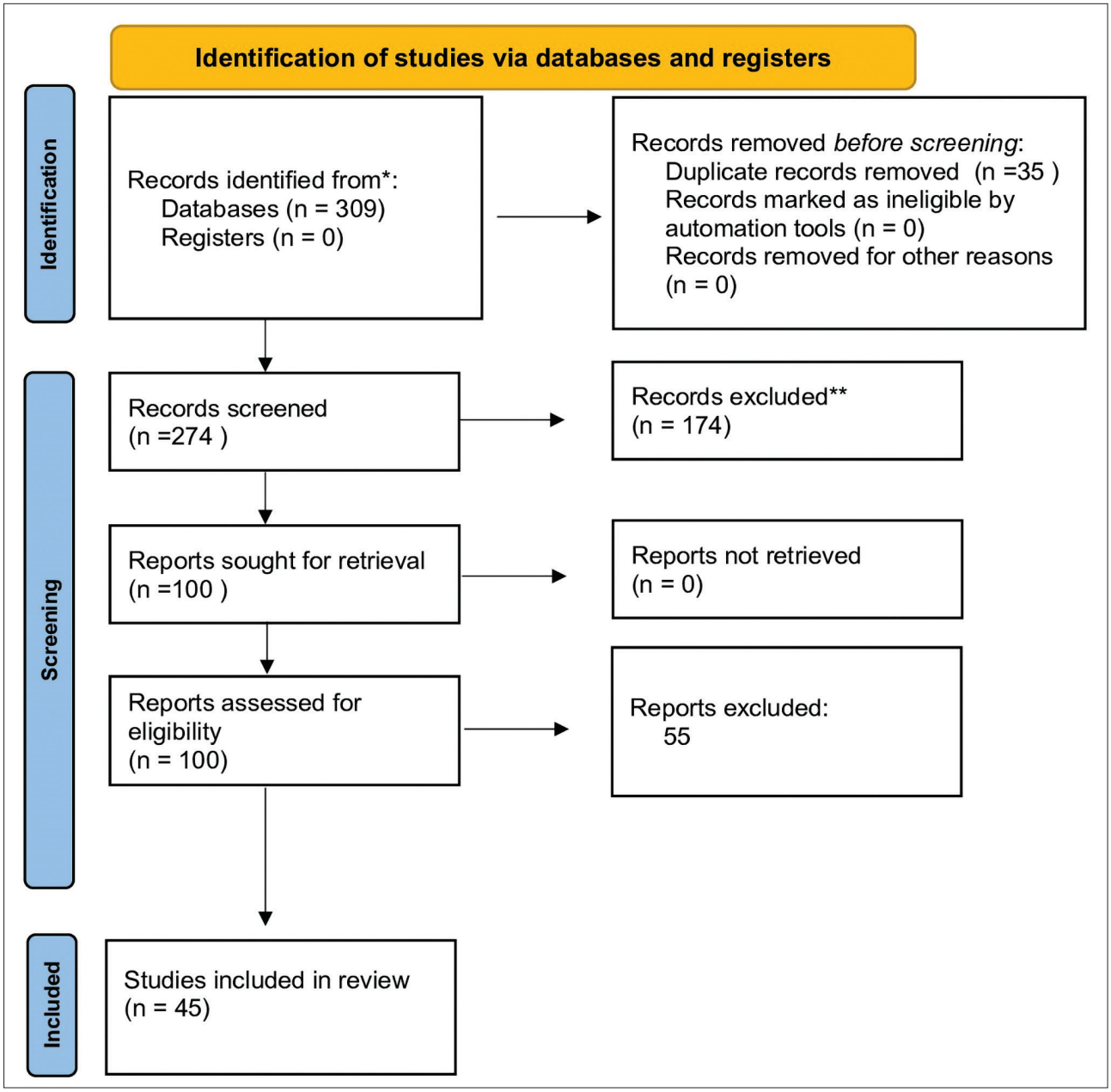
The inclusion criteria were studies focused on anti-Hu antibodies and ovarian cancer, research detailing differences between anti-Hu and other paraneoplastic antibodies in ovarian cancer patients, studies on PNS associated with any type of cancer emphasizing neurological, encephalitic, or cerebellar manifestations, and studies on PNS diagnosis and treatments. The exclusion criteria were articles not available in full text, non-English language studies, and studies not focused on clinical or translational relevance to PNS.

After removing 35 duplicate records, 274 unique records remained. These were screened based on their titles and abstracts, resulting in the exclusion of 174 records that did not meet the inclusion criteria. The full texts of the remaining 100 articles were assessed for eligibility, excluding those not focused on paraneoplastic neurological syndromes or lacking significant data. Ultimately, 45 studies were included in the qualitative synthesis, selected for their relevance, quality of evidence, and contribution to understanding paraneoplastic neurological syndromes and associated antibodies.

It is important to note that the methodology of systematic reviews differs from narrative reviews in terms of goals and approaches. Narrative reviews aim to provide a comprehensive understanding of a topic, which can include clinical cases like the one presented in this manuscript. Potential biases in narrative reviews include selection bias, publication bias, confirmation bias, and data extraction and interpretation bias. Selection bias was minimized by following a structured and transparent search strategy, including a broad range of studies and applying clear inclusion and exclusion criteria. Publication bias was addressed by including both primary and secondary research and not limiting our search to studies with positive outcomes. Confirmation bias was reduced by critically appraising all included studies and ensuring that diverse perspectives and findings were considered. Data extraction and interpretation bias was minimized by employing a systematic approach to data extraction and involving multiple reviewers to cross-check and verify the information. The scarcity of literature on anti-Hu antibodies in ovarian cancer patients limits the potential biases, as the available studies were few and could be comprehensively reviewed.

SUPPLEMENTARY FIGURE 1

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:71. doi: 10.1136/bmj.n71.

SUPPLEMENTARY DOCUMENT 2: PRISMA 2020 CHECKLIST

SECTION AND TOPIC	ITEM #	CHECKLIST ITEM	LOCATION WHERE ITEM IS REPORTED
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Main text
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Main text
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Main text
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Supp document 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Supp document 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supp document 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Supp document 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Supp document 1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Supp document 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Supp document 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Supp document 1
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Supp document 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Supp document 1
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Supp document 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Supp document 1
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Supp document 1

SECTION AND TOPIC	ITEM #	CHECKLIST ITEM	LOCATION WHERE ITEM IS REPORTED
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Supp document 1
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supp document 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	//
Study characteristics	17	Cite each included study and present its characteristics.	Supp document 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp document 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	//
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supp document 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	//
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	//
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	//
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	//
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	//
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Main text
	23b	Discuss any limitations of the evidence included in the review.	Supp document 1
	23c	Discuss any limitations of the review processes used.	Supp document 1
	23d	Discuss implications of the results for practice, policy, and future research.	Main text
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	//
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	//
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	//
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Main text
Competing interests	26	Declare any competing interests of review authors.	Main text
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	//

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.

SUPPLEMENTARY DOCUMENT 3: DIAGNOSTIC SCHEME FOR PNS

This diagnostic scheme, known as the PNS-Care Score that can be visualized on the original article (23), evaluates the likelihood of a patient having paraneoplastic syndromes based on a combination of clinical, laboratory, and cancer-related criteria. The system assigns points to different aspects of the patient's condition, summing these points to categorize the diagnostic level.

Clinical level assessment

1. **High-risk phenotypes**: patients presenting with high-risk phenotypes are awarded 3 points. These phenotypes have a strong association with PNS and indicate a higher likelihood of the syndrome.
2. **Intermediate-risk phenotypes**: if the patient exhibits intermediate-risk phenotypes, they receive 2 points. These phenotypes suggest a moderate likelihood of PNS.
3. **Defined phenotype not associated with cancer**: patients with phenotypes that are defined but not associated with cancer get 0 points, indicating a lower likelihood of PNS.

Laboratory levels

1. **High-risk antibody**: presence of antibodies that have over a 70% association with cancer grants the patient 3 points. These high-risk antibodies strongly suggest the presence of PNS.
2. **Intermediate-risk antibody**: antibodies with a 30%-70% cancer association score 2 points, indicating a moderate risk.
3. **Lower risk antibody or negative**: if antibodies have under a 30% association with cancer or if no antibodies are detected, the patient receives 0 points, indicating a lower risk of PNS.

Cancer consistency

1. **Found consistent with phenotype and antibody**: if cancer is found and it aligns with the phenotype and any present antibodies, or if antigen expression is demonstrated, the patient scores 4 points. This high score reflects a strong indication of PNS.
2. **Not found but follow-up under 2 years**: patients who have no cancer found or inconsistent findings but have been under follow-up for less than 2 years receive 1 point, indicating a need for further monitoring.
3. **Not found with follow-up over 2 years**: if no cancer is found and follow-up has exceeded 2 years, the patient gets 0 points, suggesting a very low likelihood of PNS.

Total score and diagnostic levels

After tallying the points from the clinical, laboratory, and cancer consistency assessments, the total score determines the diagnostic level:

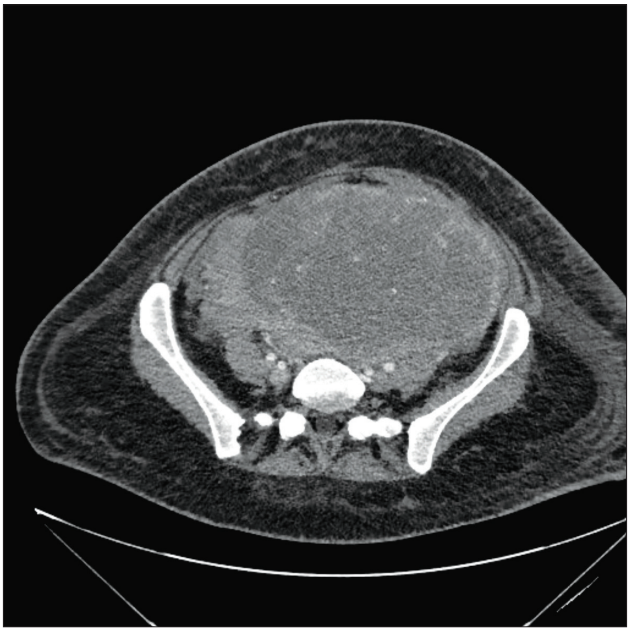
- **8 points**: definite PNS
- **6-7 points**: probable PNS
- **4-5 points**: possible PNS
- **3 points**: non-PNS

This scoring system provides a structured approach to diagnosing PNS, allowing clinicians to categorize patients based on their likelihood of having the syndrome, thereby facilitating appropriate follow-up and management.

Refer to original article: (mention as "23" in the main text) Graus F, Vogrig A, Muñiz-Castrillo S, Antoine JG, Desestret V, Dubey D, *et al*. Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes. Neurol Neuroimmunol Neuroinflamm. 2021;8(4):e1014. doi: 10.1212/NXI.0000000000001014.

SUPPLEMENTARY DOCUMENT 4: KEY IMAGING FINDING

Key image at pelvic contrast-enhanced CT reveals a heterogeneous solid mass with colliquative components, measuring approximately 22 cm in diameter, significantly occupying the lower hemiabdomen.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:71. doi: 10.1136/bmj.n71.