Scientific Research Publishing

Open Journal of Ophthalmology, 2026, 16(2), 152-165
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Extrapulmonary Small Cell Carcinoma Presenting as Bilateral Papilledema, Hyponatremia, Encephalitis, Seizures, CRMP5-IgG Reactivity, and Prominent Anterior Tubular Perivascular Spaces

Ramsis Benjamin, Drew Thomas, Nina Mourao, J. Judd Fite, Brianna Woodliff, Shubhank Goyal

Institute of Neuroscience, University of Texas Rio Grande Valley, Harlingen, USA
Email: ramsisbenjamin@gmail.com

How to cite this paper: Benjamin, R., Thomas, D., Mourao, N., Fite, J.J., Woodliff, B. and Goyal, S. (2026) Extrapulmonary Small Cell Carcinoma Presenting as Bilateral Papilledema, Hyponatremia, Encephalitis, Seizures, CRMP5-IgG Reactivity, and Prominent Anterior Tubular Perivascular Spaces. *Open Journal of Ophthalmology*, **16**, 152-165.
https://doi.org/10.4236/ojoph.2026.162015

Received: March 30, 2026
Accepted: April 27, 2026
Published: April 30, 2026

Abstract

Background: Paraneoplastic syndromes that affect both the optic disc and the brain parenchyma typically harbor antibodies directed toward CV2/collapsin response-mediator protein 5 (anti-CRMP5), amphiphysin, Ma antigen 2 (Ma2/Ta), and Yo. The most common cancers linked to anti-CRMP5 antibodies include small-cell lung carcinoma (SCLC), followed by thymoma, renal cell carcinoma, and thyroid papillary carcinoma. A long-held belief explains papilledema as related to increased pressure within the subarachnoid space or the microvascular capillaries, but intracranial pressures within the normal standard range may exist in a person with a paraneoplastic syndrome and papilledema. The glymphatic system, a central waste-clearance conduit, may play a crucial role in the development of papilledema in paraneoplastic syndromes. **Case Report:** This case illustrates a patient with extra-pulmonary small cell carcinoma and 24 months of progressive papilledema and recurrent encephalopathy in the setting of hyponatremia and generalized seizures. Two separate lumbar punctures showed lymphocytosis with normal opening pressures. Magnetic resonance imaging sequences demonstrated an empty sella and prominent tubular Virchow-Robin perivascular spaces that fan circumferentially, coined as the "Comb sign," which may be an indirect indicator of bilateral papilledema. A mass in the right adrenal gland was biopsied, which yielded small-cell carcinoma immunostaining phenotype. The patient's lumbar puncture demonstrated lymphocytosis with polyclonality, CRMP5-IgG reactivity, but negative immunoblotting. **Conclusion:** Patients presenting with insidious progressive neuro-ophthalmological symptoms should raise suspicion for paraneoplastic

syndrome, in particular, anti-CRMP5 immunoreactivity. Although intracranial pressures by lumbar puncture are within the normal limits in this case, magnetic resonance imaging sequences may elucidate distinct comb-like patterns within the Virchow-Robin spaces, indicative of elevated tone within the interstitium. The implications of negative immunoblotting with positive reactivity are discussed.

Keywords

Paraneoplastic Syndrome, Papilledema, Seizures, Encephalopathy, SIADH, Small-Cell Lung Cancer

1. Background

Optic disc edema or papilledema is believed to be caused by axoplasmic flow stasis due to intracranial pressure elevation, imposing on the subarachnoid space or on the surrounding microvascular system, which produces intraneuronal ischemia. Bilateral optic disc edema may occur due to elevated cerebrospinal fluid pressure. This elevation results from either outflow obstruction (e.g., impairment of cerebral sinus drainage) or, more rarely, from overproduction (e.g., idiopathic intracranial hypertension). The addition of encephalopathy guides the differential diagnosis to a more global etiology, such as meningoencephalitis, space-occupying lesions, dural sinus thrombosis, or Wernicke encephalopathy [1]-[3].

Papilledema occurs in 30% - 80% of patients with brain tumors, especially those located in the posterior fossa, but they typically have preserved visual acuity at onset that worsens over the course of months [3] [4]. Indirect or paraneoplastic syndromes associated with papilledema and CNS manifestations are extremely rare, perhaps on the order of 0.01% to 0.1% of all cancer patients [5] [6]. Antibodies that are most commonly discovered show affinity towards CV2/collapsin response-mediator protein 5 (anti-CRMP5), amphiphysin, Ma antigen 2 (Ma2/Ta), and Yo, often seen in patients with lung cancer and thymoma, followed by renal and thyroid papillary carcinoma [7]-[11]. Other anti-cytoplasmic antigen antibodies, such as anti-Hu (ANNA-1), anti-Ri, and anti-SOX1 antibodies, may coexist with CRMP5 antibodies in cases of small cell carcinoma, which suggests a similarity in their epitopes [12]-[14].

Limited-stage small-cell neuroendocrine carcinoma confers a poor prognosis due to its rapid cellular proliferation and a 60% - 70% metastasis rate at diagnosis. Atypical presentations include paraneoplastic syndromes such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), Lambert-Eaton myasthenic syndrome, and Cushing's syndrome.

A case of extra-pulmonary small cell carcinoma with progressive symptoms of papilledema, SIADH, encephalopathy, and seizures is presented. It carries special features of absent pulmonary findings, lymphocytosis in the CSF with polyclonality, CRMP5-IgG reactivity but negative immunoblotting, and prominent and

atypical Virchow-Robin spaces in the anterior frontal lobes on magnetic resonance imaging of the brain that are hereby designated as "Comb sign".

2. Case Report

October 2022:
Chief Complaint: Acute painless blind spots in vision
Exam: October and November – bilateral papilledema
Brain MRI negative
Lumbar punctures:
LP1 (10/27/2022): opening pressure 9 cmH_2O
CSF: glu 60, protein 67, RBC 3, WBC 68 (96% lymph)
LP2 (12/2/2022): opening pressure 14.5 cmH_2O
CSF: glu 63, protein 58, RBC 2, WBC 25 (89% lymph), flow cytology with atypical B cells suspicious for kappa light chain-restriction

2023:
Worsening vision with brief periodic right temporal headaches.
Persistent papilledema, January and February 2023.
CT chest/abdomen/pelvis 1/13/2023 negative.
Pulse high-intensity methylprednisolone without improvement in vision.

2024:
Hospitalization for acute metabolic encephalopathy due to SIADH.
CT chest/abdomen/pelvis 2/13/24 demonstrated new bilateral adrenal masses.
SARS-CoV-2 proved positive.
Readmitted 3/2024 months later for tonic-clonic seizures
Brain MRI report 3/12/2024:
1. No evidence of acute intracranial abnormality. No acute ischemia.
2. Age-related generalized cerebral and cerebellar atrophy.
3. Age-related white matter changes.

Closer inspection showed a prominent empty sella and tubular Virchow-Robin spaces.
Biopsy of the right adrenal mass was consistent with small-cell carcinoma.
The patient opted for no further treatment and requested hospice care.

NH is a patient in her 70s who smokes half a pack a day and is on prednisone therapy at 10 mg daily for COPD exacerbation. Two years earlier, she woke up with blind spots in her vision, which worsened over the course of hours to weeks in both eyes at distance and up close and were uncorrectable with glasses. Vision appeared as if seeing "through fog." The ophthalmology visit revealed bilateral papilledema, which prompted magnetic resonance sequences of the orbits and brain that revealed no clear structural abnormality. This was followed by two sequential lumbar punctures 2 months apart, showing normal opening pressures but lymphocytosis. An atypical B-cell pattern suspicious for kappa light chain restriction was noted on the second lumbar puncture test (**Table 1**). Chronic lymphocytic pleocytosis (>5 cells/mm^3) in the cerebrospinal fluid over repeated analyses signifies ongoing long-term inflammation, infection, or immune-mediated

Table 1. Pertinent ancillary testing.

Antinuclear Ab, HEp-2 Substrate, S	<1:80 (Negative)
Angiotensin-Converting Enzyme, S	28 (Nl 16 - 85 U/L)
Syphilis IgG Antibody	Nonreactive
Sed Rate (ESR)	35 (0 - 30 mm/hr)
CRP	3.9 (0.0 - 8.0 mg/L)
Cortisol	20.1 (3.0 - 22.4 µg/dL)
Osmolality, Serum	267 (273 - 304 mOsm/kg)
Osmolality, Urine	205.0 (300.0 - 800.0 mOsm/kg)
First LP	
Opening Pressure	9 cmH_2O
Glucose:Protein	60:67
RBC:WBC	3:68 (97% Lymph)
Second LP (2 months apart)	
Opening Pressure	14.5 cmH_2O
Glucose:Protein	63:58
RBC:WBC	2:25 (86% Lymph)
Flow Cytology	atypical B cells with kappa light chain restriction
NMO/AQP4 FACS, S	Negative
MOG FACS, S	Negative
Paraneoplastic Autoantibody Evaluation, Serum	**Mayo Clinic Lab, Rochester, Minnesota**
Amphiphysin ab	Negative
Anti-glial nuclear antibody type 1	Negative
Antineuronal nuclear antibody type 1	Negative
Antineuronal nuclear antibody type 2	Negative
Antineuronal nuclear antibody type 3	Negative
CRMP-5-IgG	Reactive Abnormal
Neuronal (V-G) K+ Channel Ab, S	0.00
P/Q-Type Calcium Channel Ab	0.00
PCA-1, S	Negative
PCA-2, S	Negative
PCA-Tr, S	Negative
Western Blot CRMP5	Negative

processes within the central nervous system. The patient's primary symptoms of acute visual disturbances without other chronic B-symptoms such as cough,

weight loss, fever, or meningeal signs speak against mycobacterium and fungal infections, as well as HaNDL syndrome (Headaches, Neurologic Deficits and CSF Lymphocytosis), or slow-acting viral infections (meningitis > 4 weeks), such as seen with HSV, HIV, LCM, and enteroviruses. The possibility of Primary CNS lymphoma was discounted secondary to absent cranial magnetic resonance studies. Although coronavirus can be classified as chronic meningitis, the patient had no obvious respiratory findings, including two negative CTs of the chest. Noninfectious causes include autoimmune disease, Behçet disease, malignancy, mucocutaneous lymph node syndrome (Kawasaki disease), and Vogt-Koyanagi-Harada disease (targeting melanin-producing cells in the eyes, ears, skin, and meninges). Although the last condition would produce an acute visual deficit, it also exhibits prodromal flu-like illness, meningismus, dizziness, tinnitus, poliosis, panuveitis, and exudative retinal detachments, but not papilledema. While strongly associated with multiple sclerosis, elevated Kappa free light chain (κ-FLC) can also be found in other inflammatory or infectious neurological conditions, requiring interpretation in the context of symptoms. Because of the patient's chronic tobacco dependency, a paraneoplastic condition was favored as the leading differential diagnosis.

Over the ensuing year, the patient's vision worsened. She also developed occasional upper right temple headaches lasting ~5 minutes each. A trial of high-intensity methylprednisolone produced no noticeable improvement in her vision.

Ophthalmology Findings

Upon examination, her vision was 20/70 OD and 20/70 OS BCDVA, and she had prominent bilateral optic disc edema, OD 214 μm and OS 238 μm. Macular OCT revealed inner segment/outer segment mottling in both eyes with RPE thinning and mottling without macular edema. Fundus autofluorescence revealed minimal hyperautofluorescence along the parafoveal area (**Figure 1**). CT Head revealed no acute intracranial findings except moderate global cerebral volume loss and extensive deep white matter changes consistent with chronic microvascular ischemia. Lumbar puncture revealed lymphocytic pleocytosis with an opening pressure of 9 cmH_2O, and a repeat lumbar puncture was performed to analyze flow cytometry and cytological evaluation of CSF. Flow cytometry showed atypical CD10-positive B-cells. Serological workup, including a Bartonella Antibody Panel, QuantiFERON TB, NMO IgG autoantibodies, Lyme total antibody, RPR, ESR, and CRP, was negative. The patient's vision continued to worsen to 20/250 OD and 20/150 OS BCDVA, and her optic disc edema remained persistent throughout examinations. The patient was diagnosed with extrapulmonary small cell carcinoma and was lost to ophthalmological follow-up. Hence, the case was diagnosed as paraneoplastic optic neuropathy with retinitis secondary to small-cell carcinoma.

Two months before her hospitalization, the patient presented with acute metabolic encephalopathy in the setting of euvolemic hyponatremia ($[Na^+]$ 122 nmol/L) and low serum osmolality, requiring DDAVP and 3% hypertonic saline, which corrected the sodium to 127 nmol/L. Criteria for SIADH diagnosis include a se-

rum sodium less than 135 nmol/L and the correction of hyponatremia by fluid restriction. Her encephalopathy significantly improved during hospitalization. Computed tomography of the chest, abdomen, and pelvis demonstrated bilateral adrenal nodules measuring up to 3.9 cm on the left and 3.5 cm on the right (Figure 2). Assay for SARS-CoV-2 proved positive. Steroid therapy for 5 days improved the hypoxemia, and she returned to a nursing home. She required readmission for a witnessed tonic-clonic seizure. Her systolic blood pressure was 210 mmHg. Due to an obtunded state and a Glasgow Coma Scale score of 6, the patient required emergent mechanical ventilator support. A brain MRI with contrast material again demonstrated no overt pathology except for subtle features of empty sella and prominent, diffuse tubular Virchow-Robin spaces (Figure 3). A CT-guided biopsy of the right adrenal gland was performed, consistent with small-cell carcinoma (Figure 4).

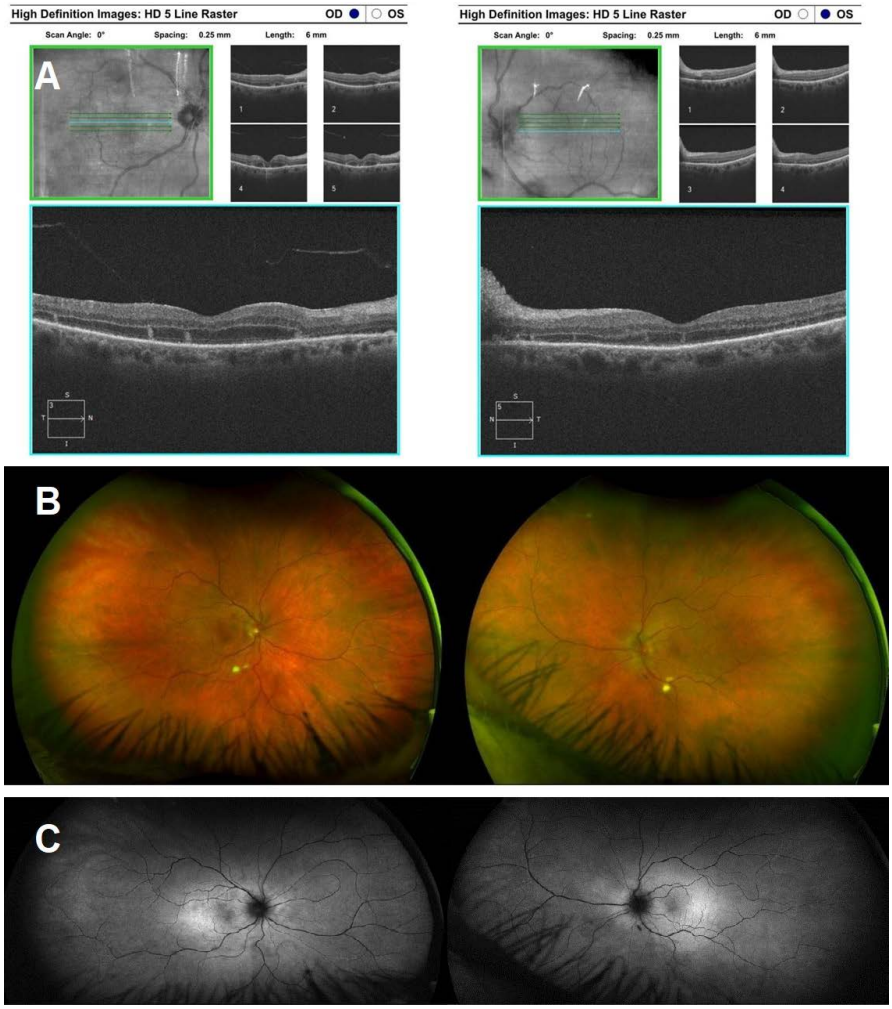

Figure 1. Ophthalmological examination of the patient. SD-OCT shows thinning of the photoreceptor layer and decreased central macular thickness (A). Disc margin obliteration is consistent with grade 3 bilateral papilledema (B). The hyper-autofluorescent parafoveal ring (bottom black-and-white panel) is more prominent in the left eye than in the right eye (C).

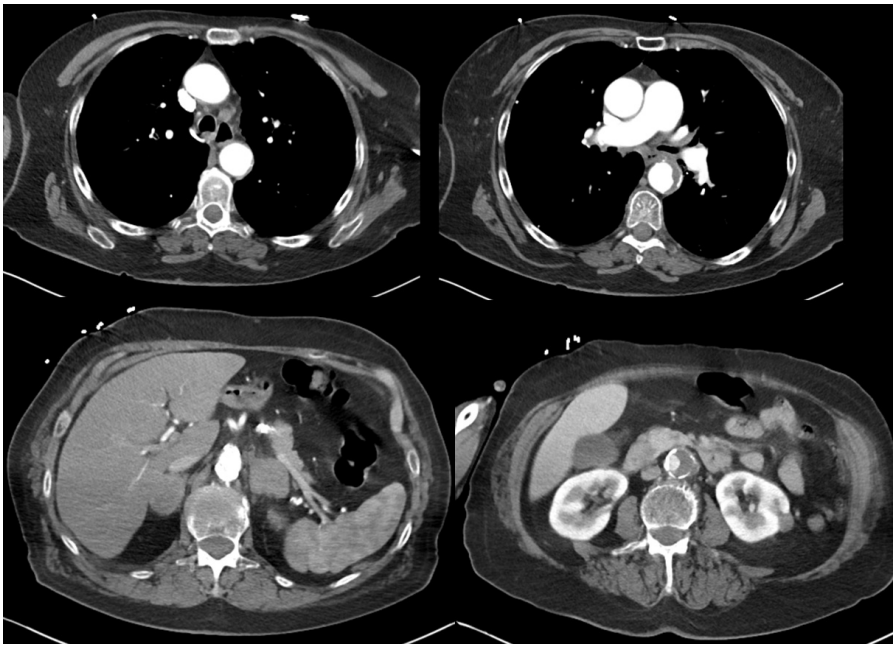

Figure 2. Computed tomography of the chest, abdomen, and pelvis. The lungs reveal no obvious pathology (A). Large bilateral adrenal nodules measure up to 3.9 cm on the left and 3.5 cm on the right. There is also an intermediate-density lesion in the lower pole of the left kidney (B).

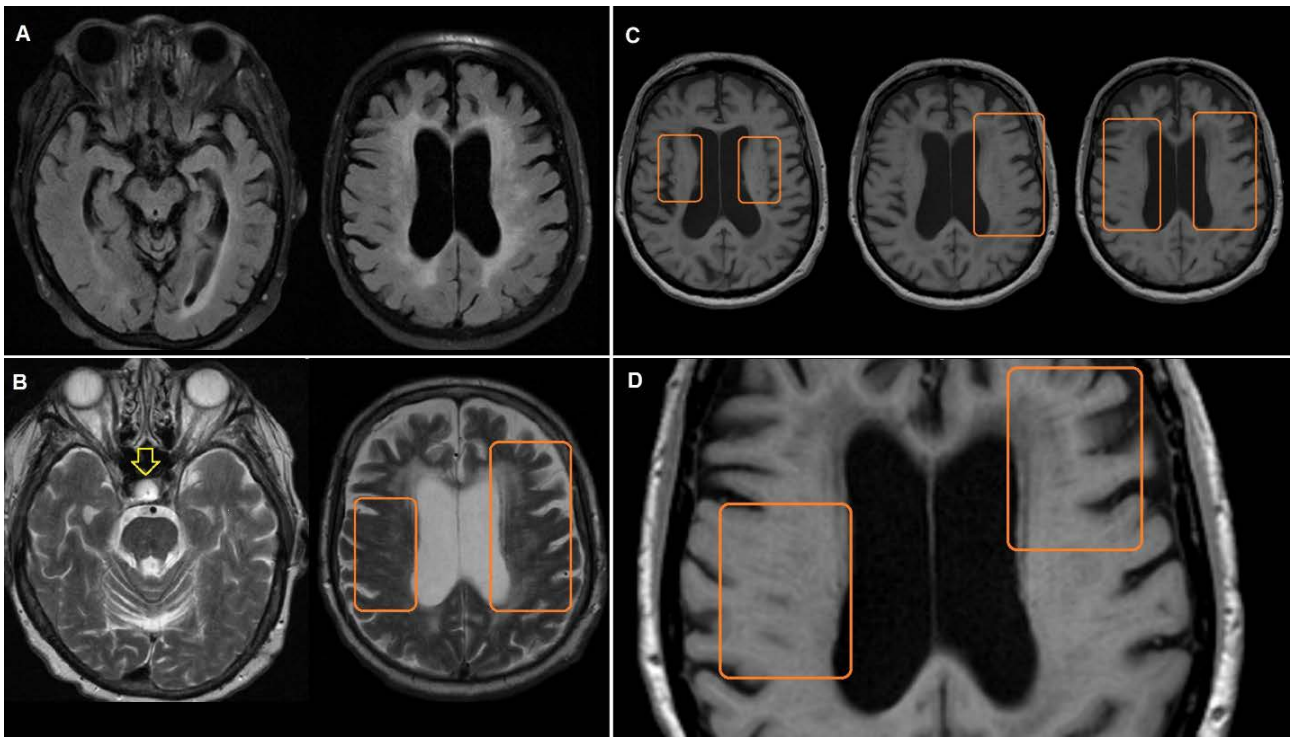

Figure 3. Axial FLAIR, T2-w, and T1-w Magnetic Resonance Images of the patient. Magnetic images using a 3-Tesla scanner, which is more sensitive to brain water content, show periventricular white matter disease on FLAIR (A), and a "Comb sign" on T2-(B) and T1-weighted (C) images, representing prominent tubular Virchow-Robin perivascular spaces of various diameters that are more anterior than posterior. One of the T1-weighted images is magnified (D) for better viewing of the tubular perivascular spaces, which disproportionately affect the anterior subcortical region. The T2-weighted sequences also reveal an empty sella (yellow arrow), which can at times be associated with pseudotumor cerebri. This patient, however, had normal CSF pressures.

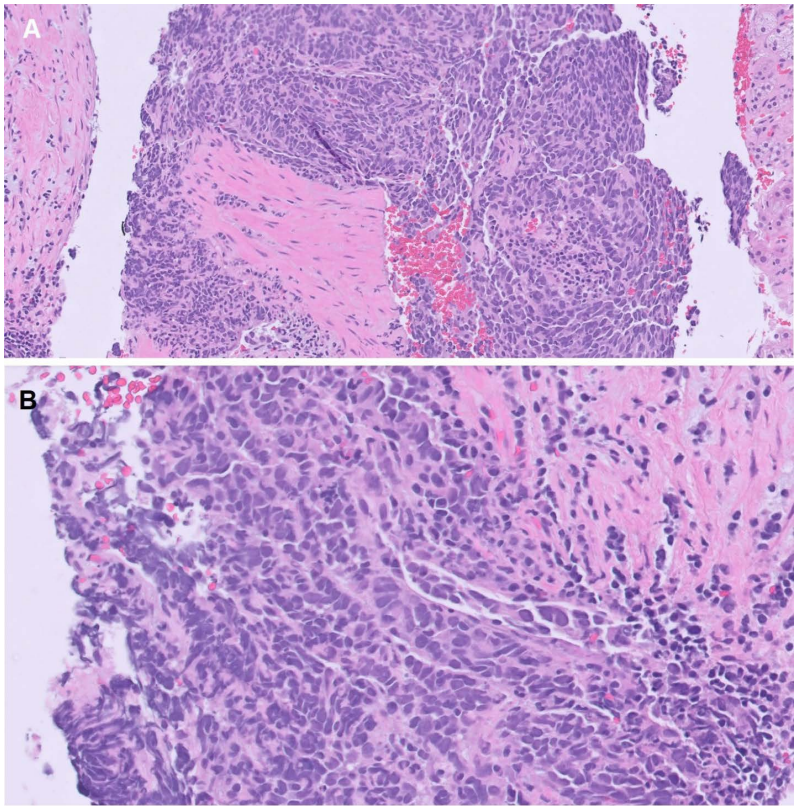

Figure 4. Pathological slides of the right adrenal mass. Biopsy of the adrenal mass is morphologically consistent with small cell carcinoma, demonstrating an increased nuclear-to-cytoplasmic ratio, nuclear molding, and finely dispersed chromatin with smudging. By immunohistochemistry, these cells are strongly positive for TTF-1, Synaptophysin, and AE1/AE3 in a dot-like pattern. TTF-1 is commonly positive in both lung and extrapulmonary small cell carcinoma. Tumor cells are negative for CK7, CK20, and CD45.

A comprehensive approach, including neurology and radiology specialties, was included in the care of this patient. The patient opted for hospice care instead of aggressive medical management and chemotherapy.

3. Methods

Hospital registration and standard protocols were applied upon admission. No experiment was conducted; therefore, a statement of approval by the Hospital Ethics Committee and Institutional Review Board was deemed not warranted. Instead, written informed patient consent via the patient's power of attorney (in this case, the patient's son) was obtained.

4. Discussion

The eye and the central nervous system consist of neurons derived from the same neural tube, with both organs possessing a barrier composed of non-fenestrated endothelial cells [15]. The traditional circulation theory of cerebrospinal fluid (CSF) homeostasis accounts for 75% of its production by the choroid plexus, which loops from the ventricles into the subarachnoid spaces. CSF, however, can

be produced and absorbed throughout the brain, and the pericapillary Virchow-Robin space exerts a bidirectional movement of the CSF between the parenchymal extracellular space and the subarachnoid space, helping to remove waste products and maintain homeostasis [16]. The Virchow-Robin space also facilitates CSF flow from the basal cisterns into the interstitial fluid [17].

The dilation of Virchow-Robin spaces (VRS) can thus be viewed as a dysregulation in the bidirectional inflow and outflow within the perivascular region. Changes occur in disease states such as increased permeability via the tight junctions of endothelial cells in vasculitis, reduced subarachnoid drainage due to structural, inflammatory, or chemical obstruction, and changes in cerebral perfusion pressure that increase intraventricular pressure [18]-[21].

Although the presence of prominent Virchow-Robin spaces alone is not pathognomonic for a specific condition, it can be a clue when combined with other clinical findings. In fact, enlarged VRS are increasingly recognized as potential imaging biomarkers of neurological conditions that disrupt cerebral homeostasis. These include vascular diseases such as hypertension, neurodegenerative disorders including Parkinson's disease, frontotemporal dementia, and cerebral amyloid angiopathy, by virtue of their causing leptomeningeal obstruction. Enlarged VRS have also been observed in immune-mediated disorders such as multiple sclerosis and neuromyelitis optica spectrum, due to their immune response at the level of the blood-brain barrier and astrocyte foot processes, and in infectious and inflammatory conditions such as sarcoidosis [22]-[29].

In the normal axial MRI plane, VRS in the periventricular region are uniform in size, with a diameter of 2-3 mm, and tubular in shape, becoming round or oval superiorly. Virchow-Robin spaces are evenly distributed in the white matter but are more numerous posteriorly [30].

In this patient, the tubular perivascular spaces illustrate disparate calibers and occupy the anterior portion of the frontal lobe, with the appearance of a comb, a subtle but perhaps significant detail given the optic disc swelling.

The expression of CRMP5 in the developing brain is restricted to the brain regions with regenerative capacity and in neuronal migration [31]. Photoreceptor cells, retinal ganglion cells, and nerve fibers show distinctive CRMP-5-specific immunoreactivity [32].

Paraneoplastic optic neuropathy (PON) is a rare disease that presents with bilateral, subacute, progressive, and painless loss of visual acuity. Abnormal ERG, VEP, and visual field defects are common. Anti-Hu and anti-CV2/CRMP5 antibodies are associated with PON [33].

Paraneoplastic syndromes commonly associated with CRMP5 antibodies include encephalomyelitis, uveo/retinal syndromes, myasthenia gravis/Lambert-Eaton myasthenic syndrome, cerebellar ataxic syndrome, and peripheral neuropathy, the last two being the most common maladies [7] [32] [34] [35].

Patients with paraneoplastic optic neuropathy and anti-CRMP5 antibodies present with painless visual deficits over the course of a few days to weeks. In time,

other symptoms manifest that include encephalopathy, seizures, sicca syndrome, various hyper- and hypokinetic movement disorders, ataxia, and failure to thrive [32] [36]. An underlying cancer can be identified in approximately three-quarters of cases with CRMP5 antibody-associated peripheral neuropathy [8], and CRMP5 antibodies often coexist with other paraneoplastic antibodies, most commonly anti-Hu [7] [34]. The majority of patients with anti-CRMP5 antibodies have small cell lung carcinoma (SCLC), and less commonly renal cell carcinoma, thyroid papillary carcinoma, cervical carcinoma, testicular seminoma, thymoma, and colonic carcinoma [37]. Mortality reaches 60% within 5 years in individuals with SCLC, and visual acuity improves in half of the treated cases with any immunomodulatory therapy [38].

In the case presented, the patient continued to smoke cigarettes. No overt lung cancer was discovered on imaging studies, although mediastinoscopy was not performed for a more direct visualization. The pathological sample from the adrenal gland was, however, consistent with metastasis from SCLC.

Lastly, the patient's immunoblot also proved negative despite the CRM5-IgG reactivity in the serum. Commercially available tissue-based Western blot assays can yield false negatives [39], with up to 7.5% of known CRM5-IgG positives by immunohistochemistry testing negative on Western blot [40]. Line blotting is a more sensitive test for CRMP5 but is diagnostically insignificant without immunohistochemistry and produces false positives [41]. If the concern for paraneoplastic syndrome remains high, other methods should be utilized. Full-length CRMP5 protein analysis in the retina, vitreous, or CSF could have been performed, but its utility was questioned as the amount of the protein may have been too infinitesimal for assay detection.

The revised Paraneoplastic Syndrome-Care Score in 2021 combines clinical phenotype, antibody type, the presence of cancer, and patient follow-up [42]. This patient falls into the high-risk category secondary to the presence of encephalomyelitis, lymphocytic leukocytosis in the CSF, and the positivity of the CV2/CRMP5 antibody, with a PNS-Care score of 10, whereby a definite diagnostic level is defined by a score of 8 and above.

5. Conclusion

This case further expands the known clinical spectrum of anti-CRMP5 paraneoplastic syndromes in the setting of small cell carcinoma. The combination of progressive painless optic neuropathy with encephalitis and seizures raises the index of suspicion for an immune-mediated disorder. A thorough systemic investigation for occult cancer, particularly neuroendocrine carcinoma, should be undertaken, as early detection and treatment improve morbidity and mortality rates.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Yeh, W., Lian, L., Chang, A. and Cheng, C. (2013) Thiamine-Deficient Optic Neuropathy Associated with Wernicke's Encephalopathy in Patients with Chronic Diarrhea. *Journal of the Formosan Medical Association*, **112**, 165-170. https://doi.org/10.1016/j.jfma.2012.10.010

[2] Gratton, S. and Lam, B. (2014) Visual Loss and Optic Nerve Head Swelling in Thiamine Deficiency without Prolonged Dietary Deficiency. *Clinical Ophthalmology*, **8**, 1021-1024. https://doi.org/10.2147/opth.s64228

[3] Lee, A., Rigi, M., Almarzouqi, S. and Morgan, M. (2015) Papilledema: Epidemiology, Etiology, and Clinical Management. *Eye and Brain*, **7**, 47-57. https://doi.org/10.2147/eb.s69174

[4] Allen, E.D., Byrd, S.E., Darling, C.F., Tomita, T. and Wilczynski, M.A. (1993) The Clinical and Radio-Logical Evaluation of Primary Brain Tumors in Children. Part I: Clinical Evaluation. *Journal of the National Medical Association*, **85**, 445-451.

[5] Parrado-Carrillo, A., Alcubierre, R., Camós-Carreras, A. and Sanchez-Dalmau, B.F. (2022) Paraneoplastic Syndromes in Ophthalmology. *Archivos de la Sociedad Española de Oftalmología* (*English Edition*), **97**, 350-357. https://doi.org/10.1016/j.oftale.2022.03.006

[6] Darnell, R.B. and Posner, J.B. (2003) Paraneoplastic Syndromes Involving the Nervous System. *New England Journal of Medicine*, **349**, 1543-1554. https://doi.org/10.1056/nejmra023009

[7] Honnorat, J., Cartalat-Carel, S., Ricard, D., Camdessanche, J.P., Carpentier, A.F., Rogemond, V., *et al.* (2009) Onco-Neural Antibodies and Tumour Type Determine Survival and Neurological Symptoms in Paraneoplastic Neurological Syndromes with Hu or CV2/CRMP5 Antibodies. *Journal of Neurology, Neurosurgery & Psychiatry*, **80**, 412-416. https://doi.org/10.1136/jnnp.2007.138016

[8] Camdessanché, J., Lassablière, F., Meyronnet, D., Férraud, K., Absi, L., Honnorat, J., *et al.* (2006) Expression of the Onconeural CV2/CRMP5 Antigen in Thymus and Thymoma. *Journal of Neuroimmunology*, **174**, 168-173. https://doi.org/10.1016/j.jneuroim.2006.01.018

[9] Zekeridou, A., Majed, M., Heliopoulos, I. and Lennon, V.A. (2019) Paraneoplastic Autoimmunity and Small-Cell Lung Cancer: Neurological and Serological Accompaniments. *Thoracic Cancer*, **10**, 1001-1004. https://doi.org/10.1111/1759-7714.13009

[10] Monstad, S.E., Drivsholm, L., Skeie, G.O., Aarseth, J.H. and Vedeler, C.A. (2008) CRMP5 Antibodies in Patients with Small-Cell Lung Cancer or Thymoma. *Cancer Immunology, Immunotherapy*, **57**, 227-232. https://doi.org/10.1007/s00262-007-0369-1

[11] Bussat, A., Langner-Lemercier, S., Salmon, A. and Mouriaux, F. (2018) Paraneoplastic Syndromes in Ophthalmology. *Journal Français d' Ophtalmologie*, **41**, e181-e185. https://doi.org/10.1016/j.jfo.2018.03.002

[12] Tschernatsch, M., Singh, P., Gross, O., Gerriets, T., Kneifel, N., Probst, C., *et al.* (2010) Anti-SOX1 Antibodies in Patients with Paraneoplastic and Non-Paraneoplastic Neuropathy. *Journal of Neuroimmunology*, **226**, 177-180. https://doi.org/10.1016/j.jneuroim.2010.07.005

[13] Schwenkenbecher, P., Chacko, L.P., Wurster, U., Pars, K., Pul, R., Sühs, K., *et al.* (2016) Intrathecal Synthesis of Anti-Hu Antibodies Distinguishes Patients with Paraneoplastic Peripheral Neuropathy and Encephalitis. *BMC Neurology*, **16**, Article No. 136. https://doi.org/10.1186/s12883-016-0657-5

[14] Carvalho Neto, E.G.D., Gomes, M.F., Alves, R.P.M., Santos, A.P.D., Brum, C. and Santin, R. (2020) Anti-RI Autoimmune Encephalitis Associated with Breast Cancer. *Arquivos de Neuro-Psiquiatria*, **78**, 737-737. https://doi.org/10.1590/0004-282x20200091

[15] Jindal, V. (2015) Interconnection between Brain and Retinal Neurodegenerations. *Molecular Neurobiology*, **51**, 885-892. https://doi.org/10.1007/s12035-014-8733-6

[16] Orešković, D. and Klarica, M. (2010) The Formation of Cerebrospinal Fluid: Nearly a Hundred Years of Interpretations and Misinterpretations. *Brain Research Reviews*, **64**, 241-262. https://doi.org/10.1016/j.brainresrev.2010.04.006

[17] Cherian, I., Beltran, M., Kasper, E., Bhattarai, B., Munokami, S. and Grasso, G. (2016) Exploring the Virchow-Robin Spaces Function: A Unified Theory of Brain Diseases. *Surgical Neurology International*, **7**, 711-714. https://doi.org/10.4103/2152-7806.192486

[18] Awad, I.A., Johnson, P.C., Spetzler, R.F. and Hodak, J.A. (1986) Incidental Subcortical Lesions Identified on Magnetic Resonance Imaging in the Elderly. II. Postmortem Pathological Correlations. *Stroke*, **17**, 1090-1097. https://doi.org/10.1161/01.str.17.6.1090

[19] Poirier, J., Barbizet, J., Gaston, A. and Meyrignac, C. (1983) [Thalamic Dementia. Expansive Lacunae of the Thalamo-Paramedian Mesencephalic area. Hydrocephalus Caused by Stenosis of the Aqueduct of Sylvius]. *Revista de Neurología*, **139**, 349-358.

[20] Caner, B., Bekar, A., Hakyemez, B., Taskapilioglu, O. and Aksoy, K. (2008) Dilatation of Virchow-Robin Perivascular Spaces: Report of 3 Cases with Different Localizations. *Minimally Invasive Neurosurgery*, **51**, 11-14. https://doi.org/10.1055/s-2007-1022538

[21] Fanous, R. and Midia, M. (2007) Perivascular Spaces: Normal and Giant. *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques*, **34**, 5-10. https://doi.org/10.1017/s0317167100005722

[22] Doubal, F.N., MacLullich, A.M.J., Ferguson, K.J., Dennis, M.S. and Wardlaw, J.M. (2010) Enlarged Perivascular Spaces on MRI Are a Feature of Cerebral Small Vessel Disease. *Stroke*, **41**, 450-454. https://doi.org/10.1161/strokeaha.109.564914

[23] Ramirez, J., Berezuk, C., McNeely, A.A., Scott, C.J.M., Gao, F. and Black, S.E. (2015) Visible Virchow-Robin Spaces on Magnetic Resonance Imaging of Alzheimer's Disease Patients and Normal Elderly from the Sunnybrook Dementia Study. *Journal of Alzheimer's Disease*, **43**, 415-424. https://doi.org/10.3233/jad-132528

[24] Potter, G.M., Doubal, F.N., Jackson, C.A., Chappell, F.M., Sudlow, C.L., Dennis, M.S., *et al.* (2015) Enlarged Perivascular Spaces and Cerebral Small Vessel Disease. *International Journal of Stroke*, **10**, 376-381. https://doi.org/10.1111/ijs.12054

[25] Charidimou, A., Jaunmuktane, Z., Baron, J., Burnell, M., Varlet, P., Peeters, A., *et al.* (2014) White Matter Perivascular Spaces: An MRI Marker in Pathology-Proven Cerebral Amyloid Angiopathy? *Neurology*, **82**, 57-62. https://doi.org/10.1212/01.wnl.0000438225.02729.04

[26] Ingrese, M., Bomsztyk, E., Gonen, O., Mannon, K.J., Grossman, R.I. and Rusinek, H. (2005) Dilated Perivascular Spaces: Hallmarks of Mild Traumatic Brain Injury. *American Journal of Neuroradiology*, **26**, 719-724.

[27] Charidimou, A., Boulouis, G., Pasi, M., Auriel, E., van Etten, E.S., Haley, K., *et al.* (2017) MRI-Visible Perivascular Spaces in Cerebral Amyloid Angiopathy and Hypertensive Arteriopathy. *Neurology*, **88**, 1157-1164. https://doi.org/10.1212/wnl.0000000000003746

[28] Kim, S., Na, H.K., Sun, Y., Yoon, Y.J., Chung, S.J., Sohn, Y.H., *et al.* (2024) Regional Burden of Enlarged Perivascular Spaces and Cognition and Neuropsychiatric Symptoms

in Drug-Naive Patients with Parkinson Disease. *Neurology*, **102**, e209483. https://doi.org/10.1212/wnl.0000000000209483

[29] Moses, J., Sinclair, B., Schwartz, D.L., Silbert, L.C., O'Brien, T.J., Law, M., *et al.* (2022) Perivascular Spaces as a Marker of Disease Severity and Neurodegeneration in Patients with Behavioral Variant Frontotemporal Dementia. *Frontiers in Neuroscience*, **16**, Article 1003522. https://doi.org/10.3389/fnins.2022.1003522

[30] Ishikawa, M., Yamada, S. and Yamamoto, K. (2015) Three-Dimensional Observation of Virchow-Robin Spaces in the Basal Ganglia and White Matter and Their Relevance to Idiopathic Normal Pressure Hydrocephalus. *Fluids and Barriers of the CNS*, **12**, Article No. 15. https://doi.org/10.1186/s12987-015-0010-1

[31] Yan, J., Chen, Z., Liang, Y., Yang, H., Cao, L., Zhou, Y., *et al.* (2020) Anti-CV2/CRMP5 Antibody-Positive Paraneoplastic Neurological Syndromes with Chronic Intestinal Pseudo-Obstruction in a Small-Cell Lung Cancer Patient: A Case Report and Literature Review. *Journal of International Medical Research*, **48**. https://doi.org/10.1177/0300060520974466

[32] Cross, S.A., Salomao, D.R., Parisi, J.E., Kryzer, T.J., Bradley, E.A., Mines, J.A., *et al.* (2003) Paraneoplastic Autoimmune Optic Neuritis with Retinitis Defined by CRMP-5-IgG. *Annals of Neurology*, **54**, 38-50. https://doi.org/10.1002/ana.10587

[33] Rosencher, L., Maisonobe, T., Lavole, A., Milleron, B. and Ferroir, J.P. (2012) Syndrome neurologique paranéoplasique à anticorps anti-CV2/CRMP5 révélateur d'un cancer bronchique à petites cellules. Efficacité du traitement du cancer bronchique. *Revue Neurologique*, **168**, 371-374. https://doi.org/10.1016/j.neurol.2011.07.016

[34] Dubey, D., Lennon, V.A., Gadoth, A., Pittock, S.J., Flanagan, E.P., Schmeling, J.E., *et al.* (2018) Autoimmune CRMP5 Neuropathy Phenotype and Outcome Defined from 105 Cases. *Neurology*, **90**, e103-e110. https://doi.org/10.1212/wnl.0000000000004803

[35] Totland, C., Haugen, M. and Vedeler, C. (2021) CRMP5 Antibodies—Diagnostic Challenges. *Frontiers in Neurology*, **12**, Article 729075. https://doi.org/10.3389/fneur.2021.729075

[36] Hickman, S.J. (2022) Paraneoplastic Syndromes in Neuro-Ophthalmology. *Annals of Indian Academy of Neurology*, **25**, S101-S105. https://doi.org/10.4103/aian.aian_102_22

[37] Xu, Q., Du, W., Zhou, H., Zhang, X., Liu, H., Song, H., *et al.* (2019) Distinct Clinical Characteristics of Paraneoplastic Optic Neuropathy. *British Journal of Ophthalmology*, **103**, 797-801. https://doi.org/10.1136/bjophthalmol-2018-312046

[38] Cohen, D.A., Bhatti, M.T., Pulido, J.S., Lennon, V.A., Dubey, D., Flanagan, E.P., *et al.* (2020) Collapsin Response-Mediator Protein 5-Associated Retinitis, Vitritis, and Optic Disc Edema. *Ophthalmology*, **127**, 221-229. https://doi.org/10.1016/j.ophtha.2019.09.012

[39] Vandenbussche, N., Cassiman, C., Schrooten, M., Gille, B., Bossuyt, X., Vincent, T., *et al.* (2017) Negative Commercial Screening Test for Paraneoplastic Antibodies in a Case of Opsoclonus. *Neurology Neuroimmunology & Neuroinflammation*, **4**, e329. https://doi.org/10.1212/nxi.0000000000000329

[40] Sabater, L., Saiz, A., Dalmau, J. and Graus, F. (2016) Pitfalls in the Detection of CV2 (CRMP5) Antibodies. *Journal of Neuroimmunology*, **290**, 80-83. https://doi.org/10.1016/j.jneuroim.2015.11.009

[41] Ruiz-García, R., Martínez-Hernández, E., Saiz, A., Dalmau, J. and Graus, F. (2020) The Diagnostic Value of Onconeural Antibodies Depends on How They Are Tested. *Frontiers in Immunology*, **11**, Article 1482. https://doi.org/10.3389/fimmu.2020.01482

[42] Graus, F., Vogrig, A., Muñiz-Castrillo, S., Antoine, J.G., Desestret, V., Dubey, D., *et al.* (2021) Updated Diagnostic Criteria for Paraneoplastic Neurologic Syndromes. *Neurology Neuroimmunology & Neuroinflammation*, **8**, e1014. https://doi.org/10.1212/nxi.0000000000001014