Paraneoplastic Myeloneuropathies
Clinical, Oncologic, and Serologic Accompaniments

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Abstract

Objective
To test the hypothesis that myeloneuropathy is a presenting phenotype of paraneoplastic neurologic syndromes we retrospectively reviewed clinical, radiologic, and serologic features of 32 patients with concomitant paraneoplastic spinal cord and peripheral nervous system involvement.

Methods
Observational study investigating patients with myeloneuropathy and underlying cancer or onconeural antibody seropositivity.

Results
Among 32 patients with paraneoplastic myeloneuropathy, 20 (63%) were women with median age 61 years (range 27–84 years). Twenty-six patients (81%) had classified onconeural antibodies (amphiphysin, n = 8; antineuronal nuclear antibody [ANNA] type 1 [anti-Hu], n = 5; collapsin response mediator protein 5 [CRMP5] [anti-CV2], n = 6; Purkinje cell cytoplasmic antibody type 1 [PCA1] [anti-Yo], n = 1; Purkinje cell cytoplasmic antibody type 2 [PCA2], n = 2; kelch-like protein 11 [KLHL11], n = 1; and combinations thereof: ANNA1/CRMP5, n = 1; ANNA1/amphiphysin, n = 1; ANNA3/CRMP5, n = 1). Cancer was confirmed in 25 cases (onconeural antibodies, n = 19; unclassified antibodies, n = 3; no antibodies, n = 3). Paraneoplastic myeloneuropathies had asymmetric paresthesias (84%), neuropathic pain (78%), subacute onset (72%), sensory ataxia (69%), bladder dysfunction (69%), and unintentional weight loss >15 pounds (63%). Neurologic examination demonstrated concomitant distal or asymmetric hyporeflexia and hyperreflexia (81%), impaired vibration and proprioception (69%), Babinski response (68%), and asymmetric weakness (66%). MRI showed longitudinally extensive (45%), tract-specific spinal cord T2 hyperintensities (39%) and lumbar nerve root enhancement (38%). Ten of 28 (36%) were unable to ambulate independently at last follow-up (median 24 months, range 5–133 months). Combined oncologic and immunologic therapy had more favorable modified Rankin Scale scores at post-treatment follow-up compared to those receiving either oncologic or immunologic therapy alone (2 [range 1–4] vs 4 [range 2–6], p < 0.001).

Conclusions
Paraneoplastic etiologies should be considered in the evaluation of subacute myeloneuropathies. Recognition of key characteristics of paraneoplastic myeloneuropathy may facilitate early tumor diagnosis and initiation of immunosuppressive treatment.
Myeloneuropathies are defined by the concomitant development of peripheral nerve and spinal cord involvement.1,2 Etiologies usually associated with myeloneuropathy include metabolic (vitamin B₁₂ or copper deficiency), inflammatory, infectious, hereditary, or toxic. Paraneoplastic neurologic syndrome diagnostic criteria (2004) included paraneoplastic encephalomyelitis, limbic encephalitis, cerebellar degeneration, subacute sensory neuronopathy, and chronic gastrointestinal pseudo-obstruction as classical paraneoplastic phenotypes.3 Paraneoplastic myelopathy and sensorimotor neuropathy were individually described as non-classical syndrome but paraneoplastic myeloneuropathy was not specifically described.

Paraneoplastic association was defined by presence of onconeural autoantibody in the serum with >70% neoplastic association or a diagnosis of neoplasm within 3 years of symptom onset and exclusion of alternative causes such as multiple sclerosis or neuromyelitis optica spectrum disorder.3 Furthermore, patients with vitamin B₁₂ or copper deficiency, HIV infection, prominent neuropathy attributed to chemotherapy by historical documentation, and neoplastic infiltration of the CNS were excluded.

Search terms used to identify cases included myeloneuropathy, paraneoplastic myelopathy, paraneoplastic neuropathy, paraneoplastic sensory neuronopathy, paraneoplastic polyradiculoneuropathy, paraneoplastic motor neuron disease, and paraneoplastic encephalomyelitis. Laboratory databases by discrete onconeural antibody positivity (collapsin response mediator protein 5 [CRMP5], ANNA1, amphiphysin, Purkinje cell cytoplasmic antibody [PCA] type 2) and cancers (breast adenocarcinoma, small cell lung cancer, testicular cancer) were also used to identify patients.7,18–23 Medical records of patients who met the stated criteria were reviewed by 3 neurologists (S.S., R.V.D.C., D.D.) for demographic, clinical, electrophysiologic, and radiographic data. Outcomes were measured by ambulatory status and by change in modified Rankin Scale (mRS) score before treatment and at last follow-up in those patients with available outcome data. A decrease in mRS scores of ≥1 was considered to be a favorable response.

**Methods**

**Standard Protocol Approvals, Registration, and Patient Consents**

The study was approved by the institutional review board of Mayo Clinic, Rochester, Minnesota (institutional review board number 08-006647). Electronic medical records and neuroimmunology laboratory databases between 1995 and 2019 were used to identify patients with clinical, radiographic, or electrodiagnostic evidence of myelopathy and peripheral neuropathy.15–17

Patients with concomitant development of peripheral nerve or root, and spinal cord involvement within a 3-month timeframe with supporting evidence of multifocal involvement in both clinical and radiographic or electrodiagnostic domains were included. Cases with coexisting encephalopathy at onset or isolated motor neuron involvement were excluded.

**Laboratory Methods**

All patients were evaluated for onconeural antibodies to various specificities: ANNA1, ANNA2, ANNA3, CRMP5, antiglial/neuronal nuclear antibody (AGNA1, or SOX1), amphiphysin, PCA1, microtubule-associated protein 1B antibody (MAP1B; PCA2), and kelch-like protein 11 (KLHL11) in the Mayo Clinic Neuroimmunology Laboratory.17–19,22,24,25

**Indirect Immunofluorescence Assay for Antibody Detection**

Patient sera were tested by indirect tissue-based indirect immunofluorescence on a cryosectioned (4 μm) composite of adult mouse cerebellar, midbrain, cerebral cortex, hippocampus,
kidney, and gut tissue, as previously described. Samples with characteristic staining patterns were titrated in doubling dilutions to determine the endpoint titer.

Recombinant Protein Western Blot/HEK293 Cells Overexpression Assay
Amphiphysin, MAP1B, and CRMP5 antibody specificities were confirmed by Western blot analysis using recombinant human amphiphysin protein (full length), MAP1B fragment (amino acids 1–666), and CRMP5 (full-length), respectively. KLHL11 IgG detected on tissue immunofluorescence was confirmed by KLHL11 HEK293 overexpression cell-based assay.

Statistical Analysis
Descriptive data were reported using medians, ranges, and percentages. Categorical and continuous variables were analyzed by Mann-Whitney U testing. The p value was 2-sided and p values less than 0.05 were significant (JMP Pro 14).

Data Availability
All Methods are available above and data are published in this article.

Results
Demographics, Antibody, and Oncologic Associations
Thirty-two patients had paraneoplastic myeloneuropathy as their initial presentation (table). Twenty were women (63%) and median age was 61 years (range 27–84 years). Chronic tobacco use was noted in 81% of patients (median 40 packs per year, n = 26). Underlying malignancy was detected in 25 patients. Small cell lung cancer (n = 11) and breast adenocarcinoma (n = 7) were the most common malignancies, with further details shown in figure 1. Neurologic symptoms manifested prior to cancer diagnosis in 22/25 patients and the remaining 3 cases had symptom onset within 3 years of cancer diagnosis.

Among 32 patients with paraneoplastic myeloneuropathy, 20 had antibody evaluations in the serum and 12 had both serum and CSF neural-specific antibody testing. Twenty-six had detectable onconeural antibodies: amphiphysin, n = 8 (serum only, n = 4; CSF and serum, n = 4; median serum titer 1:3,840; range 1:240–1:24,576 [normal < 1:120]; median CSF titer 1:64, range 1:4–1:960 [normal < 1:4]); ANNA1 (anti-Hu), n = 5 (serum only, n = 4; CSF and serum, n = 1, median serum titer 1:3,840, range 1:240–1:122,880; CSF titer 1:512); CRMP5, n = 6 (serum only, n = 3; CSF and serum, n = 3, median serum titer 1:3,840, range 1:240–1:491,520; median CSF titer 1:512, range 1:64–1:192); PCA1 (anti-Yo), n = 1 (serum titer 1:240; CSF titer 1:16); PCA2 (MAP1B), n = 2 (serum only, titers 1:240; 1:15,360); KLHL11, n = 1 (serum titer 1:240 and CSF titer 1:4); and combinations thereof: ANNA1/CRMP5, n = 1 (serum titer 1:960/1:240); ANNA1/amphiphysin, n = 1 (serum titer 1:61,440/1:30,720; CSF titer 1:4/1:1,024); ANNA3/CRMP5, n = 1 (ANNA3 serum titer 1:960, CRMP5 detected in both serum and CSF, serum titer 1:7,680 and CSF titer 1:1,024). Nineteen of these 26 patients were diagnosed with cancers. The remaining 7 patients had imaging findings suggestive of neoplasm, but pathologic confirmation was not available (figure 1). Among these, 1 patient had a breast mass, 4 had lung masses, and 2 had abdominal masses. Biopsy and histopathologic analysis in 2 of these 7 cases was nondiagnostic. In 3 patients, data regarding biopsy/histopathologic evaluation of the mass was not present in the patient records. In 2 patients, rapid neurologic deterioration and superimposed infection led to death prior to attempting biopsy. All 6 patients without characterized onconeural antibodies (unclassified neural specific antibodies, n = 3 [2 detected in serum, and 1 detected in both serum and CSF]) had pathologically confirmed cancer.

Clinical Characteristics
Patients frequently had a subacute presentation, defined as nadir of symptom severity occurring 1 to 3 months from onset (n = 23, 72%). Two patients (6%) presented acutely within 1 month and 7 (22%) presented with a more chronic decline. Most common clinical characteristics included neuropathic pain (n = 25, 78%), bladder dysfunction (n = 22, 69%), asymmetric paresthesias (n = 20, 63%), and unintentional weight loss of greater than 15 pounds (n = 20, 63%; median weight loss 20 pounds [range 15–75]). Neuropathic symptoms were non-length-dependent (n = 28, 88%) and radicular involvement was noted in 56% (n = 18) of patients. Patients commonly had cramping, spams, or stiffness (n = 17, 53%), and in 2 patients with amphiphysin autoantibodies, simultaneous peripheral nerve hyperexcitability. Orhtostatic intolerance defined by clinical history of syncope or lightheadedness and blood pressure changes upon standing was seen in 14 patients (44%) with supportive autonomic reflex testing in 4 patients. Gastrointestinal dysmotility at onset, defined as new, severe postprandial fullness or nausea, constipation, or diarrhea (n = 14, 44%) was also common; 1 patient had gastric motility studies, which demonstrated prolonged colonic and small bowel emptying.

Neurologic examination commonly demonstrated simultaneous hyporeflexia and hyperreflexia at different sites (n = 26, 81%). Hyporeflexia was usually present distally or in an asymmetric pattern. The majority of patients also had impaired vibration and proprioception (n = 22, 69%), Babinski response (n = 22, 68%), and asymmetric weakness (n = 21, 66%). Weakness was noted in both upper and lower limbs in 44% of patients (n = 14). Thirty-seven percent (n = 12) of patients had isolated lower limb involvement and 19% (n = 6) had isolated upper limb involvement.

Copper or vitamin B12 deficiency related subacute combined degeneration was the primary diagnostic consideration at disease onset in 28 patients (88%) but was excluded by pertinent laboratory investigation. Among patients with CSF analysis (n = 28), the majority (23, 82%) had inflammatory
MRI Characteristics of Patients With Paraneoplastic Myeloneuropathy

Several notable imaging findings were observed, and representative images are provided in figure 2. Imaging was not available for review in 1 patient. Spinal cord T2 hyperintensities were present in 19 patients (61%), and 14 (45%) were longitudinally extensive (≥3 vertebral segments) T2 lesions (table). Twelve patients (39%) did not demonstrate any spinal cord MRI abnormalities, despite myelopathic findings on examination. T2 hyperintensities were tract-specific in 12 of the 19 (63%) abnormal MRIs and dorsal columns (n = 6), lateral corticospinal tract (n = 5), or both dorsal column and corticospinal tracts (n = 1) (figure 2). Central gray matter abnormalities were also identified in 9 patients (29%). Half of the tract-specific lesions (n = 6, 50%) had bilaterally symmetric involvement of the spinal cord tracts. Approximately one-third of patients (n = 11, 35%) demonstrated active contrast extravasation. Ten patients (32%) demonstrated nerve root contrast enhancement, limited to the lumbar roots (figure 2).

Neuropathy Characteristics

Electrodiagnostic studies were performed in 31 patients, and all had electrophysiologic features suggestive of an axonal neuropathy. One patient additionally had some features of demyelination on nerve conduction studies, presumed secondary to axonal loss. One patient with clinically evident neuropathy did not undergo electrodiagnostic study. Clinical description of neuropathic pain radiating down one or more dermatomal distributions with proximal muscle weakness or evidence of denervation in the paraspinal muscles was considered indicative of radicular involvement. Polyradiculoneuropathy with evidence of nerve root and peripheral nerve involvement was the most common neuropathy phenotype (n = 16, 50%), closely followed by distal, asymmetric sensorimotor neuropathy (n = 10, 31%). Sensory ganglionopathy and symmetric length-dependent sensorimotor neuropathies were present in 2 and 4 patients, respectively.

Somatosensory evoked potentials performed in 2 patients demonstrated impairment in both central and peripheral proprioceptive pathways. Autonomic reflex testing was performed in 4 patients. Two patients had moderate to severe cardiovagal, adrenergic, and postganglionic sudomotor dysfunction. One had adrenergic and postganglionic sudomotor dysfunction and another had moderate to severe cardiovagal and adrenergic impairments with preserved postganglionic sudomotor function, suggesting a limited autonomic failure.

Management and Clinical Outcomes

Ten patients received only immunotherapy, 3 received only oncologic therapy, and 16 received both. First-line immunotherapies included 1 or more of the following: high-dose IV methylprednisolone (n = 19), IV immunoglobulin (n = 12), oral prednisone (n = 12), or plasmapheresis (n = 4). A subset of these patients received long-term immunosuppression: cyclophosphamide (n = 9), rituximab (n = 2), mycophenolate...
mofetil (n = 2), and azathioprine (n = 2). Three seropositive patients without pathologic diagnosis of neoplasm did not receive oncologic or immunologic therapy.

Median duration of follow-up was 24 months (range 5–133 months). Fifteen of 28 patients (53%) with long-term follow-up (>1 year follow-up) had favorable clinical outcomes with cancer treatment or immunotherapy at subsequent follow-up. Another 6 patients stabilized, whereas 7 continued to deteriorate despite therapy. At last known follow-up, 7 patients (22%) had died. Median follow-up for patients without identified malignancies was 11 months (range 10–20).

Figure 1 Cancer and Onconeural Antibody Associations

(A) Summary of onconeural antibodies and presence of cancer; 3 patients had unclassified neural specific antibodies. (B) Cancer association in 25 patients. Among 7 patients, no neoplasms were identified. ANNA1 = antineuronal nuclear antibody type 1 (anti-Hu); ANNA3 = antineuronal nuclear antibody type 3; CRMP5 = collapsin response mediator protein 5 (CV2); PCA1 = Purkinje cell cytoplasmic antibody type 1; KHLH11 = kelch-like protein 11.

Figure 2 MRI Spine Abnormalities in Paraneoplastic Myeloneuropathies

Cervical, thoracic, and lumbar spine MRI sagittal (A.a, B.a, C.a, D.a) and axial (A.b, B.b, C.b, D.b) sequences. (A.a, A.b) Collapsin response mediator protein 5 (CRMP5) (CV2) immunoglobulin G (IgG)–seropositive adult patient with asymmetric, longitudinally extensive T2-hyperintense lesion (white arrow) involving the right corticospinal tracts (blue arrow) with a concomitant axonal polyradiculoneuropathy. (B.a, B.b) Antineuronal nuclear antibody type 1 (anti-Hu) (ANNA1) and amphiphysin IgG–seropositive adult patient with longitudinally extensive T2-hyperintense lesion (white arrow) involving the right dorsal column (blue arrow) with a concomitant sensory predominant length dependent axonal polyneuropathy. (C.a, C.b) ANNA1 IgG–seropositive adult patient with symmetric, bilateral, longitudinally extensive T2-hyperintense lesion (white arrow) involving the dorsal columns (blue arrows) and concomitant sensory predominant length dependent axonal polyneuropathy. (D.a, D.b) Adult patient with unclassified neural specific antibody with diffuse nerve roots enhancement on post-gadolinium T1-weighted sagittal (white arrow) and axial (blue arrow) sequences.
In patients receiving a combination of oncologic and immunologic therapy, outcomes were significantly favorable (median change in mRS before and after treatment) in comparison to those receiving either oncologic or immunologic therapy alone (−2 [range −3 to 0] vs 0 [range −1 to 2], p < 0.001). Furthermore, median mRS at posttreatment follow-up among the patients receiving combination therapy was significantly lower than patients receiving either oncologic or immunologic therapy alone (2 [range 1–4] vs 4 [range 2–6] p < 0.001).

Discussion

Paraneoplastic myeloneuropathies exist as their own unique clinical phenotype and may be a diagnostic consideration in the evaluation of myeloneuropathies. Key presenting features of paraneoplastic myeloneuropathy are subacute asymmetric weakness and paresthesias, severe neuropathic pain, sensory ataxia, bladder dysfunction, and orthostatic intolerance. Examination reveals concomitant hyporeflexia and hyperreflexia, Babinski response, asymmetric weakness and numbness, and impaired vibration and proprioception. Diagnostic workup was remarkable for longitudinally extensive, tract-specific T2-hyperintense spinal cord lesions, spinal cord or nerve root gadolinium enhancement, and inflammatory CSF. In this study, wheelchair dependence at disease nadir among patients with paraneoplastic myeloneuropathy was noted in a little more than half of the patients.

Gastrointestinal dysmotility and orthostatic intolerance seen in several patients was similar to previously reported paraneoplastic neuropathy studies. This may be primarily due to postganglionic autonomic nerve dysfunction, as suggested by the quantitative sudomotor axon reflex screen. However, dysfunction of sympathetic or parasympathetic preganglionic neuronal tracts within the spinal cord may also have some contribution.

Some of these distinguishing characteristics, especially sensory ataxia, have been highlighted in prior case reports of paraneoplastic myeloneuropathies. Longitudinally extensive tract-specific changes on MRI have been similarly reported in a patient with seronegative paraneoplastic myeloneuropathy associated with breast cancer. Autoimmune myeloneuropathies without a strong oncologic association have also been described among patients with adaptor protein 3B2 autoimmunity and Sjögren syndrome.

In our study, small cell lung cancer and breast adenocarcinoma were the most common oncologic associations (53%), similar to prior reports of paraneoplastic myelopathies or neuropathies. The majority of cancers were detected at an early stage (n = 18, 72%), supportive of either a potent anticancer immune response or indicative of earlier cancer detection due to paraneoplastic neurologic manifestations. ANNA1, CRMP5, and amphiphysin were the most common autoantibody specificities noted (figure 1). Intracellular localization of the autoantigens for the majority of these antibodies supports the significant role of autoantigen-specific T-cell response among these cases. These findings demonstrate that paraneoplastic myeloneuropathy presentation, similar to other classic or nonclassic paraneoplastic phenotypes, can be seen in association with various onconeural antibodies and cancers.

Comprehensive neuropathologic analysis of well-characterized paraneoplastic myeloneuropathy is lacking. However, histopathologic assessment of spinal cord and nerve biopsies of patients presenting with paraneoplastic myelopathy or neuropathy has demonstrated perivascular cuffing of CD8+ T lymphocytes, supporting a cytotoxic T cell–mediated pathogenesis. Concern may exist regarding immunosuppression reducing anticancer response or potential drug interactions with other cancer chemotherapies; however, the majority of patients with myeloneuropathy who received early, combined cancer and immunosuppressive therapy had favorable long-term clinical outcomes. This dual approach of removal of antigen source and immune response suppression has been successfully utilized in classical PNS.

Paraneoplastic myeloneuropathy phenotype differs from paraneoplastic motor neuron disease, due to predominance of sensory involvement. Due to lack of encephalitis among these cases, the term “encephalomyelitis” does not provide accurate information about the neurologic localization of this paraneoplastic phenotype. Longitudinally extensive tract-specific MRI findings (figure 2) are common among paraneoplastic myeloneuropathies, and have also been described in isolated paraneoplastic myelopathies. These radiographic features are distinct from demyelinating diseases such as multiple sclerosis, which are characterized by shorter segment, asymmetric lesions. Copper deficiency can present with myeloneuropathy with symmetric dorsal column abnormalities on imaging, but can be distinguished by its chronic disease course and lack of associated neuropathic pain. Other notable radiographic findings such as central gray matter involvement and gadolinium enhancement of the intramedullary spinal cord and nerve roots can also help distinguish this syndrome from metabolic myeloneuropathies. It is important to note that few patients with paraneoplastic myeloneuropathy did not have imaging abnormalities but had other supportive clinical and paraclinical findings including inflammatory CSF supportive of immune-mediated pathogenesis.

This is a retrospective study and some cases had limited long-term follow-up data. A limitation of this approach includes the potential to overlook this entity if clinical diagnosis or identifiable terminology was not included in clinical documentation, particularly patients in whom diagnostic evaluations were performed between several institutions. Longer follow-up and
repeated cancer screenings may have provided more definitive evidence of neoplasm and highlights the importance of the guideline-driven approach to repeat testing at 6- to 12-month intervals for 2 years when suspecting paraneoplastic neurologic syndrome.3,40,41

The observations from our study may provide insights into this rare yet distinguishable paraneoplastic phenotype.14 Clinical recognition of this subacute myeloneuropathy phenotype may result in early cancer diagnosis, and favorable neurologic outcomes with combined oncologic and immunosuppressive therapy.

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Disclosure
Shailee Shah, Rocio Vazquez Do Campo, and Neeraj Kumar report no relevant disclosures. Andrew McKeon has a patent pending for KLHLL1, Septin 5, and MAP1B as markers of neurologic autoimmunity and paraneoplastic disorders. Eoin P. Flanagan is a site principal investigator in a randomized placebo-controlled clinical trial of inebilizumab (a cluster of differentiation 19 inhibitor) in neuromyelitis optica spectrum disorders funded by MedImmune/Viela Bio and receives research funding from the NIH, National Institute of Neurologic Disorders and Stroke (R01NS113828). Christopher Klein reports no relevant disclosures. Sean J. Pittock is a named inventor on a patent in functional AQP4/NMO-IgG assays and NMO-IgG as a cancer marker; has a patent pending for KLHLL1-IgG, Septin 5, and MAP1B IgGs as markers of neurologic autoimmunity and paraneoplastic disorders; has consulted for Alexion and Medimmune; and has received research support from Grifols, Mediimmune, and Alexion. All compensation for consulting activities is paid directly to Mayo Clinic. Divyanshu Dubey has a patent pending for KLHLL1-IgG as a marker of neurologic autoimmunity. Go to Neurology.org/N for full disclosures.

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Appendix (continued)

| Name                  | Location | Contributions                          |
|-----------------------|----------|----------------------------------------|
| Rocio Vazquez Do Campo, MD | Mayo Clinic | Acquired the data, interpreted the data, revised the manuscript for intellectual content |
| Neeraj Kumar, MD      | Mayo Clinic | Interpreted the data, revised the manuscript for intellectual content |
| Andrew McKeon, MD     | Mayo Clinic | Interpreted the data, revised the manuscript for intellectual content |
| Eoin P. Flanagan, MD  | Mayo Clinic | Interpreted the data, revised the manuscript for intellectual content |
| Christopher Klein, MD | Mayo Clinic | Interpreted the data, revised the manuscript for intellectual content |
| Sean J. Pittock, MD   | Mayo Clinic | Interpreted the data, revised the manuscript for intellectual content |
| Divyanshu Dubey, MD   | Mayo Clinic | Designed and conceptualized study, analyzed the data, drafted the manuscript, revised the manuscript for intellectual content, study supervision |

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Appendix Authors

| Name                  | Location | Contributions                          |
|-----------------------|----------|----------------------------------------|
| Shailee Shah, MD      | Mayo Clinic | Acquired the data, analyzed the data, interpreted the data, drafted the manuscript, revised the manuscript for intellectual content |

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