A Case of Paraneoplastic Neurological Syndrome Expressing Dual Antineuronal Antibodies: Anti-Hu and Recoverin

Sir,

Paraneoplastic neurological syndromes (PNS) are a group of heterogeneous disorders that are not caused by direct invasion or metastasis but are caused by cancers outside the central or peripheral nervous system.\(^1\) In the literature, small cell lung cancer (SCLC) is commonly associated with PNS expressing various antineuronal antibodies, such as anti-Hu, anti-Ri, anti-CV2, anti-VGCC, or anti-recoverin.\(^1,2\) PNS can be in the form of cerebellar degeneration, encephalomyelitis, or sensory neuronopathy as well as retinopathy and often precedes the diagnosis of cancer.\(^1,3\) Conversely, a single antineuronal antibody can be expressed by various cancers. For example, anti-Ri antibody can be identified in breast, gynecological, or SCLC malignancies.\(^1\) Therefore, potentially, a single systemic cancer can express multiple antineuronal antibodies and vice versa. In this case report, we present an unusual case of dual expression of anti-Hu and recoverin associated with the pathologically identified SCLC.

A 65-year-old man had visited the department of neurology presenting gait disturbance with postural instability, 2 days after an influenza immunization. He had no infectious symptoms, such as fever or chills. He had a sensory abnormality for 7 years as a residual symptom owing to a spinal cord trauma below the T10 level. He had a smoking history of 67.5 pack-years. He denied any weight loss or exposure history to toxic materials associated with the symptoms. His vital signs were normal. On neurological examination at admission, mild dysarthria, limb ataxia, and positive Romberg’s test were performed. Pinprick below the T10 level and vibration sensation below the anterior superior iliac spine were disturbed, which were most likely due to the previous spinal cord trauma. Deep tendon reflexes (DTRs) of the right biceps, bilateral triceps, knee, and ankle were decreased to 1+, while the left biceps jerk reflex was absent. Ocular movements and motor functions of the limbs were normal. The laboratory blood test result was normal. In addition, the results of the analysis of the cerebrospinal fluid for infection, cell cytology, protein, and glucose were normal except for an elevated white blood cell count, 36 cells/\(\mu L\). A chest X-ray revealed no abnormal findings. Magnetic resonance images of the brain were normal except a few small dot-like lesions in the white matter suggesting leukoaraiosis [Figure 1a]. The nerve conduction study (NCS) outcomes were normal except for no response in the sensory component of the bilateral medial plantar nerves. A diagnosis of incomplete Miller Fisher syndrome was presumed based on the acute findings of limb ataxia, positive Romberg’s sign, and decreased DTR after the influenza vaccination, although extraocular movement was not impaired. Subsequently, these symptoms were managed conservatively, and the patient was transferred to the department of rehabilitation for physical therapy.

Two months after the development of symptoms, the patient showed truncal ataxia and aggravated ataxic gait. A follow-up neurological examination revealed moderate dysarthria and purely horizontal spontaneous left-beating nystagmus. Based on the medical research council’s grading system, bilateral proximal leg weakness was 4+, proximal left arm weakness was 4, and generalized absent DTR except for the right biceps and knee jerk was 1+. Limbic and truncal ataxia and a tendency to fall in the Romberg’s test was observed. There were no differences between the findings of sensory examinations compared with previous examinations. The follow-up NCS showed a decreased compound motor action potential (CMAP) amplitude for the face and four limbs, although the sensory study remained normal. These clinical and electrophysiological findings led us to an extensive investigation. The level of neuron specific enolase was normal at 9.36 ng/mL (normal range, 4.7–14.7 ng/mL). Chest computerized tomography revealed enlarged lymph nodes in the right paratracheal, prevascular, subcarinal, and hilar areas without any evidence of carcinomas in the lung parenchyma at the time of work-up [Figure 1b]. However, the test for antineuronal antibody detected both anti-Hu and recoverin antibodies, present at the same time, using the antigen-coated immunoblot method (EUROIMMUN AG, Lübeck, Germany). The histopathological examination of the right lower paratracheal lymph node using endobronchial ultrasound-guided transbronchial needle aspiration confirmed SCLC [Figure 1c and d]. The detection of the anti-recoverin antibody furthered an ophthalmologic evaluation, although the patient did not complain about any visual symptoms. On ophthalmologic examination, bilateral visual acuity was determined as 0.32. Results of the color vision test and fundus examination were normal. Ophthalmologic evaluations revealed inferonasal quadrantanopia of the left eye from Goldmann visual field test [Figure 2a], mild leakage superonasal to the fovea from fluorescein angiography [Figure 2b], and hyperreflective lesion in the outer plexiform and outer nuclear layers corresponding to the leakage area from optical coherence tomography [Figure 2c], suggesting retinopathy. The patient was not treated with chemotherapy because of the poor Eastern Cooperative Oncology Group performance status scale of 3. Methylprednisolone (1 g/day) was intravenously administrated for 5 days; however, the symptoms did not improve.

Although, initially, we had suspected incomplete Miller Fisher syndrome based on the symptoms of limb ataxia, positive Romberg’s sign, and decreased DTR, progressive deterioration of gait, limb, truncal ataxia, nystagmus, and dysarthria led to
the investigation of PNS, which could be diagnosed based on the presence of antineuronal antibody and confirmed using a pathological assessment.

Two unique features were noted in our patient. First, the presence of two types of antineuronal antibodies was noted. It is well known that PNS are associated with anti-Hu antibody. Clinically, paraneoplastic encephalomyelitis, paraneoplastic cerebellar degeneration (PCD), sensory neuronopathy, or autonomic dysfunction have been reported. However, patients with cancer-associated retinopathy (CAR) associated with anti-recoverin antibody have been seldomly reported; therefore, systemic findings of CAR have not been described effectively. Few case reports have included retinal hemorrhage and attenuated retinal arteriole with visual symptoms of field defects or decreased acuity. Ophthalmological findings in our patient are also similar to those of previously reported cases. Regardless of the type of CAR antibodies, CAR typically presents with an asymmetric, progressive loss of vision over days to years affecting both the cones and rods.

Second, the patient had presented with electrophysiologically featured axonal motor neuropathy. The sensory abnormality identified from the neurologic examination is most likely due to the previous spinal cord trauma. Because the findings of the sensory NCS were normal, gait ataxia was attributed to PCD. Decreased CMAP amplitude from the NCS corresponds with bilateral weakness of the limbs, despite the discrepancy between the clinical symptoms and electrophysiological findings. The motor neuropathy associated with anti-Hu antibody could have been more frequent than we had recognized. In their study, Oh et al. identified the involvement of the motor nerve in all enrolled patients, and low CMAP was more frequently observed than slow motor nerve conduction velocity, although most patients had shown sensory-motor neuropathy. In terms of axonal motor neuropathy, findings in our patient corresponded to those obtained in the previous report.

Here, we report a case of anti-Hu antibody associated with PCD and motor axonopathy and anti-recoverin antibody associated with retinopathy, which share a common systemic cancer, SCLC. Therefore, the involvement of more than one system should be considered in a patient with PNS.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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Acute Ischemic Stroke Due to Multiple Bee Stings: A Delayed Complication

Sir,

Bee and wasp stings may rarely cause acute stroke. We present a case of a 41-year-old man who had a fatal right MCA territory stroke following an attack by over 50 bees.

This particular 41-year-old man with no previous comorbidities was attacked by over 50 bees while at the fields and lost consciousness. He was taken to a hospital where the stings were removed and symptomatic treatment with analgesics, corticosteroids and antihistamines was provided. With treatment, he regained consciousness and was walking independently. He was kept under observation.

Five hours later, patient developed sudden onset left hemiparesis and dysarthria with gaze preference to the right side. CT head showed massive right MCA territory infarction. He was managed with dual antiplatelets. In spite of this, his sensorium deteriorated and he was started on low molecular weight heparin on the next day. He was also given intravenous mannitol. However, the patient continued to deteriorate and had to be endotracheally intubated. He was also given hyperventilation. However, the edema related to the infarct led to midline shift and the patient relatives refused surgery for decompression hemicraniectomy. The patient succumbed on the third day following the bee stings.

Bee stings are commonly associated with local reactions like erythema, edema, redness and pain at the local site which are self-limiting. It may be associated with systemic effects such as anaphylaxis including hypotension and laryngeal edema. In a series of 322 cases of wasp and bee stings reported by Witharana and colleagues, 79% had only local reaction and 4.6% developed anaphylaxis. None of them developed stroke or renal dysfunction. Only two patients had to be referred to tertiary care centre, of whom one had ocular stings and other had more than 1000 stings.

Bee stings are managed symptomatically. The first step is to remove the stings so that further exposure to the venom is stopped. Adrenaline, antihistamines and corticosteroids are usually administered to counteract local reaction as well as anaphylaxis. Patients who recover from anaphylaxis usually do not develop further symptoms. Rarely patients may develop organ dysfunction such as acute kidney injury, rhabdomyolysis, cardiac dysfunction including heart block, Takotsubo cardiomyopathy, myocardial infarction etc.

Stroke associated with bee stings are limited to a handful of case reports only. It may occur in the post-acute phase within 4 to 10 hours. Most of the reported cases are due to multiple bee stings. The exact etiology of stroke following bee sting has not been elucidated. Proposed mechanisms are 1. Due to hypotension and reduced cerebral perfusion due to anaphylaxis, 2. Hypercoagulable state and platelet aggregation due to thromboxane A2 and phospholipase activation, 3. Vasoconstriction due to retrograde stimulation of the superior cervical ganglion and carotid spasm etc.

Stroke following bee sting is very rare. Clinical history and examination is of utmost importance in diagnosing the etiology of altered sensorium and stroke. In cases of multiple bee stings, patients often become unconscious and may not be able to provide history. Our patient was brought to the hospital in an unconscious state by the passersby. In such cases, careful general examination would reveal insect bite marks which would lead to the diagnosis. Awareness of...