Autoimmune Pain due to CASPR2 Responsive to Tocilizumab

Dear Editor,

A 54-year-old man presented with a burning sensation below his knees which gradually progressed over 3 months A short-form McGill Pain Questionnaire returned a total McGill Pain Score of 31/45 (sensory subscore: 23/33, affective subscore: 8/12, Visual Analog Scale [VAS] score of 9/10).[1] Over the last month, he had started to notice a burning sensation over the palms as well. He was severely disabled and in constant pain. He had no past history of diabetes mellitus, thyroid disorders, alcohol or substance abuse, family history, or exposure to chemotherapy. On examination, he had erythromelalgia, allodynia below the wrist and hips, an antalgic gait, and normal deep tendon and plantar reflexes. Nerve conduction studies were normal, but Sudoscan (electrical skin conductance) testing was severely abnormal in the hands and legs, consistent with a small fiber neuropathy. Routine blood evaluation, including thyroid functions, glycated hemoglobin (HbA1c), B12 levels, Angiotensin converting enzyme (ACE) levels, Antinuclear antibody (ANA) profile, Antineutrophilic cytoplasmic antibody (C-ANCA), and perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA), and computed tomography (CT) thorax were normal. Viral serology (HIV, Hepatitis B surface antigen (HbsAg), hepatitis C virus [HCV]) was negative. Magnetic resonance imaging (MRI) T1-weighted images of the whole spine showed diffuse hypointensity of all vertebrae. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) computed tomography (CT) showed diffuse increased FDG uptake in the bone marrow. Bone marrow examination showed 8% plasma cells, an M band 0.3 g/dl, and elevated erythrocyte sedimentation rate (ESR; 75 mm/h) and C-reactive protein (CRP) 25 mg/dl. A provisional diagnosis of monoclonal gammopathy of undetermined significance was initially considered. He was treated with intravenous (IV) methylprednisolone 1 g/day for 5 days, rituximab 375 mg/m^2 (two doses), and cyclophosphamide × two doses. He had transient improvement (total McGill Pain Score of 25/45 and VAS score of 6/10) for 10 days, following which his pain returned. He was started on 60 mg of prednisolone/day, 600 mg pregabalin, Lupirtin 400 mg/day, and tapentadol 100 mg/day. However, his pain remained at a total McGill Pain Score of 29/45 and a VAS score of 8/10. After 6 months of therapy, he was severely disabled and unable to work. On examination, he was obese, cushingoid, had mild proximal muscle weakness, severe tenderness of his quadriceps muscles and glove, and stocking allodynia.

Nine months into his illness, serum contactin-associated protein-like 2 (CASPR2) antibody was tested and it returned strongly positive on three occasions. Other paraneoplastic and antineuronal antibodies were negative. Fabry's disease was ruled out by a dried blood spot test (measuring alpha-galactosidase enzyme activity). Nerve biopsy (to rule out amyloidosis and vasculitis) showed only nonspecific changes.

He initially underwent six cycles of plasmapheresis over 12 days. However, his VAS score only dipped to 7/10.

He received another two doses of rituximab over the next month. As there was no improvement, he was started on tocilizumab injections 800 mg subcutaneously (s/c). Within 2 weeks, his pain VAS score improved to 2/10 and by 6 weeks, it was 1/10. He received another six doses of tocilizumab injections 800 mg s/c every 2–2.5 months. After 1.5 years, he was totally asymptomatic and stopped tocilizumab and all his pain medications. Three months later, he came back with a relapse (total McGill Pain Score of 33/45 with a VAS score of 8/10). He was restarted on tocilizumab injections 800 mg s/c along with gabapentin, tapentadol, and pregabalin. Within 4 weeks, his symptoms again improved. Since then, he has been on regular bimonthly tocilizumab injections 800 mg s/c along with pregabalin 225 mg/day with good pain relief (total McGill Pain Score of 3/45 and VAS 0–1/10 score). The last follow-up was 2.5 years after starting tocilizumab. There was no change in his M band concentrations 3 years after the onset of illness.

The voltage-gated potassium channel (VGKC) complex proteins consist principally of leucine-rich glioma-inactivated 1 protein (LGI1) and CASPR2. CASPR2 neuropathy is a painful autoimmune neuropathy with a partial responsiveness to immunotherapy. An inward rectifying channel (potassium/sodium hyperpolarization-activated cyclic nucleotide-gated ion channel 2) is an important regulator of nociceptive pain.[2] Neuronal VGKCs act synergistically with these cation channels to maintain nociceptive afferent sensory neural thresholds. The axonal membrane at the juxtaparanodes contains hetero-multimers composed of Kv1.1, Kv1.2 complexes, which stabilize conduction and help to maintain the internodal resting potential.[3] CASPR2 adheres to these complexes, and the soma of C-fiber nociceptors that express VGKC current blockade may enhance neuronal excitability. LGI1 antibodies bind to Kv1.1 at the presynaptic nerve terminals and lead to central sensitization.[4]

Autoimmune pain is usually subacute or chronic in the course, regional or diffuse, and misdiagnosed as fibromyalgia or psychogenic causes. Although conventional nerve conduction studies are normal, the newer electrical skin conductance testing helps to noninvasively identify small fiber neuropathy. Additional symptoms of neuronal hyperexcitability, such as hyperhidrosis and erythromelalgia such as in our patient, also help to confirm the organic nature of pain. Other manifestations of peripheral nerve hyperexcitability (cramps, myokymia, and fasciculations) and encephalopathic manifestations such as cognitive impairment and seizures may also be present.

Autoimmune pain is usually excruciating and requires polytherapy with combinations of nonsteroidal anti-inflammatory drugs, narcotics, antiepileptics, and membrane-stabilizing medications. However, these are often ineffective without immunotherapy (oral prednisone), IV methylprednisolone, IV immune globulin (IVIg), methotrexate, and hydroxychloroquine. More than 80% of patients report improvement in pain after a mean follow-up of 18 weeks. After induction therapy, >60% of patients require maintenance therapy with low-dose steroids or other immunosuppressants. Pain improvement may correlate with a reduction in VGKC Ab-IgG levels. Other rare neuropathic pain syndromes, such as progressive encephalomyelitis with rigidity and myoclonus (PERM), also respond to immunotherapy.[1]

Treatments proposed for refractory autoimmune encephalitis include[1] cytokine-based drugs (tocilizumab, interleukin-2/basiliximab, anakinra, and tofacitinib);[2] plasma cell–depleting agents (bortezomib and daratumumab); and[3] agents that target intrathecal immune cells or their trafficking through the blood–brain barrier (intrathecal methotrexate or natalizumab).[5]

Tocilizumab, a humanized monoclonal antibody, targets soluble and membrane-bound interleukin (IL)-6 receptors and prevents IL-6 binding and signaling. Due to the crucial role of IL-6 in stimulating both B and T cells, it has been used in autoimmune encephalitis and CASPR2 encephalitis refractory to rituximab.[6,7]

Idiopathic pain, in VGKC-complex CASPR2 antibody syndrome, is reported in 50% of patients. It may also be the only manifestation of CASPR2 disease in up to 28% of these cases.[2] Hence, CASPR2 antibody-related autoimmune pain should be considered in cases of unexplained neuropathic or diffuse pain conditions. If autoimmune pain is unresponsive to conventional immunotherapy, tocilizumab can be tried.

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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Supplementary Table 1: Reported cases of *TMEM63A*-related mutation

Author, year of publication	Number of patients/sex	Clinical features	Genetic variant	Neuroimaging features
Yan *et al*., 2019[5]	4/Male: female=3:1	All patients developed symptoms in the neonatal period. Congenital nystagmus, developmental delay, pyramidal signs, ataxia, myopia, optic atrophy seen Favorable course with neurological improvement	Heterozygous missense variant, three *de novo*: c. 1699G>A [p.Gly567Ser], c. 1385T>A [p.Ile462Asn], c. 503G>A [p.Gly168Glu]; one inherited paternally: c. 1699G>A [p.Gly567Ser]	Severe myelin deficit in brain, resembling Pelizaeus–Merzbacher disease Radiological improvement concordant with clinical improvement noted
Tonduti *et al*., 2021[6]	1/Female	Congenital nystagmus from birth, developmental delay, cerebellar signs, paroxysmal unilateral eyelid twitching	Missense *de novo* variant c. 1675T>C [p.Tyr559His]	Severe hypomyelination on MRI brain and dorsal and lateral column hypomyelination along the entire spinal cord
Fukumura *et al*., 2022[4]	1/Female	Global developmental delay, hypotonia, autonomic seizures	Missense *de novo* variant c. 1658G>T [p.(Gly553Val)]	Hypomyelination with no change over 4 years of follow-up

MRI=magnetic resonance imaging