Neurología 40 (2025) 807—811

NEUROLOGÍA

www.elsevier.es/neurologia

LETTER TO THE EDITOR

Sensory neuronopathy in a patient with anti-FGFR3 antibodies and lung adenocarcinoma, coincidence or causality?

Neuronopatía sensitiva en paciente con anticuerpos anti-FGFR3 y adenocarcinoma de pulmón, ¿casualidad o causalidad?

Dear Editor:

Sensory neuronopathy (SN), or sensory ganglionopathy, is a rare subtype of peripheral neuropathy characterised by damage to the soma of peripheral sensory neurons in the dorsal root ganglia, the Gasserian ganglion, and the enteric nervous system.[1—3]

We present the case of a 57-year-old man with history of smoking, seronegative cutaneous lupus erythematosus, and pulmonary sarcoidosis under treatment with corticosteroids. Following SARS-CoV-2 infection and subsequent vaccination, he developed subacute onset of paraesthesias and neuropathic pain, which slowly progressed in a proximal direction affecting all 4 limbs. Symptoms eventually caused gait instability and impaired manual dexterity. The examination revealed impaired proprioception, generalised areflexia, and sensory ataxia. Sensory nerve conduction studies revealed a marked decrease in sensory nerve action potential (SNAP) amplitudes, with a mild decrease in conduction velocity, predominantly affecting the upper limbs, suggesting a non-length-dependent pattern. The ulnar sensory-motor amplitude ratio (USMAR)[4] was 0.24, supporting the diagnosis of SN. H-reflexes and somatosensory evoked potentials were also abnormal (Fig. 1). Motor nerve conduction studies, needle electromyography, autonomic function testing, and spinal cord MRI yielded normal results. Serological testing revealed positivity for anti-FGFR3 antibodies, while results for onconeural antibodies (anti-Hu, anti-Yo[PCA-1], anti-Ri, anti-CV2/CRMP5, anti-PNMA2[Ma2/Ta], anti-amphiphysin, anti-recoverin, anti-SOX1, anti-Zic4, anti-GAD65, anti-Tr[DNER], anti-titin), neuronal surface antibodies (anti-NMDAR, anti-GABABR, anti-AMPA, anti-LGI1, anti-CASPR2, anti-DPPX), and anti-ganglioside antibodies were all negative. Cerebrospinal fluid (CSF) analysis revealed pleocytosis (20 cells/μL; 98% lymphocytes) and elevated protein level (63.2 mg/dL). A CT scan of the neck, chest, abdomen, and pelvis revealed a pulmonary nodule in the right lower lobe with mediastinal lymphadenopathy. Positron emission tomography revealed hypermetabolism in these areas (Fig. 2). Biopsy of the lesion confirmed a diagnosis of lung adenocarcinoma. Based on these findings, the patient was diagnosed with immune-mediated SN of paraneoplastic and/or dysimmune origin associated with anti-FGFR3 antibodies.

Damage to the soma of peripheral sensory neurons may result from paraneoplastic, inflammatory, viral, toxic/nutritional, or genetic causes.[1—3,5] The most frequently identified aetiology of SN is paraneoplastic, and is considered one of the high-risk phenotypes of paraneoplastic neurological syndromes.[6] The onconeural antibodies most frequently associated with paraneoplastic SN are anti-Hu, anti-CV2/CRMP5, and anti-amphiphysin antibodies,[2,3,5,6] which are present in up to 90% of patients,[3,7] usually in association with small cell lung carcinoma, Hodgkin lymphoma, and other carcinomas.[5—7] However, despite exhaustive aetiological work-up, no cause is identified in up to 50% of cases,[5] although a underlying dysimmune origin is suspected in nearly half of them.[8] The systemic autoimmune disease most frequently associated with SN is Sjögren syndrome, with positivity for anti-SSA antibodies.[5,9] However, other systemic autoimmune diseases may also be associated with small-fibre neuropathy, which should be considered in the differential diagnosis.[10] Recent anti-AGO and anti-FGFR3 antibodies in up to 13% and 15%-19% of patients with SN, respectively.[3,5,11,12] Debate is ongoing as to whether these antibodies play a pathogenic role in SN or rather act as biomarkers of the underlying dysimmune process.[5,13] To date, no prior cases of SN with positive anti-FGFR3 antibodies and lung cancer have been reported in the literature, while the association between anti-FGFR3 antibodies and sarcoidosis in patients with SN has only rarely been described.[13] Therefore, the relationship between anti-FGFR3 antibodies and lung adenocarcinoma is yet to be established. In our patient, it is unclear whether SN was caused exclusively by anti-FGFR3 antibodies in the context of other immune processes (sarcoidosis and cutaneous lupus erythematosus) or by a seronegative paraneoplastic

DOI of refers to article: https://doi.org/10.1016/j.nrl.2024.08.001.

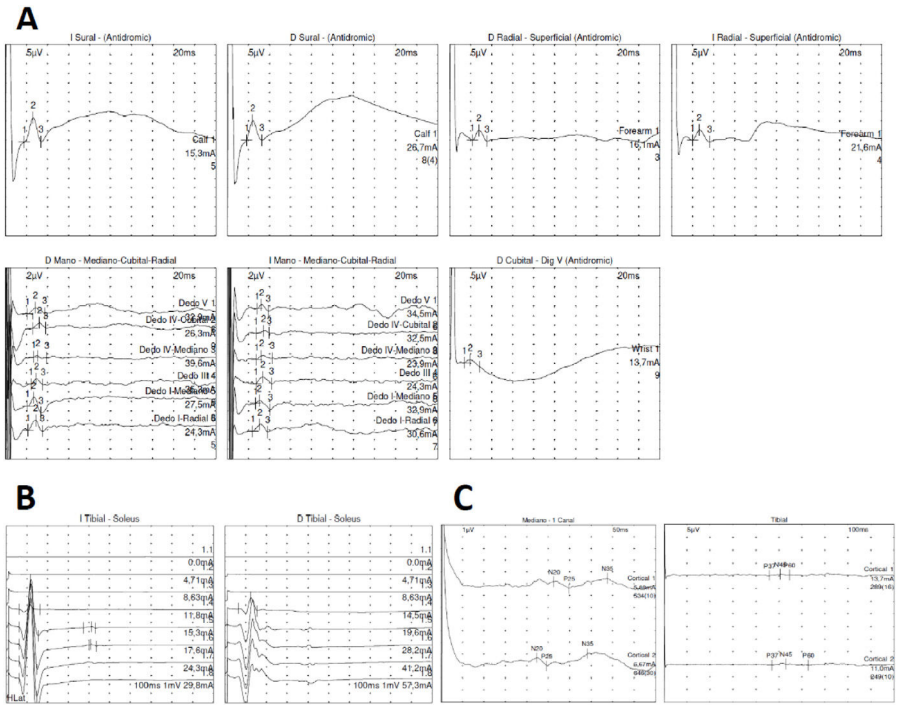

Figure 1 Neurophysiological study including sensory nerve conduction study (A), H-reflex testing (B), and somatosensory evoked potentials (C).

The images illustrate a part of the neurophysiological evaluation conducted on the patient. A) Sensory nerve conduction in the upper limbs (bilateral median, ulnar, and radial nerves) and lower limbs (bilateral sural nerves). The upper limbs show a decrease in sensory nerve action potential amplitudes, associated with diffuse slowing of conduction velocities consistent with secondary axonal damage. These findings are observed in both orthodromic and antidromic studies, indicating non—length-dependent fibre involvement. B) The H-reflexes are absent bilaterally. C) Somatosensory evoked potentials show decreased amplitude and delayed latencies bilaterally in the lower limbs. In the upper limbs, pathological responses were detected on the right side, characterised by delayed latencies and less well-defined waveforms compared to the contralateral side, revealing clear asymmetry.

syndrome, or whether anti-FGFR3 antibodies were of paraneoplastic origin and were therefore associated with both SN and lung adenocarcinoma. Further research is needed to determine this association.

Among the limitations of this study, we were unable to analyse antibody production by the tumour in the pathological specimen.

In conclusion, this case shows that multiple potential causes of SN may coexist in a single patient. In paraneoplastic cases,where tumor-directed therapy is critical, early diagnosis is particularly necessary due to its vital prognostic implications. Hence, thorough malignancy screening should be conducted even in the absence of onconeural antibodies, as up to 10% of cases may be seronegative or associated with other, known or unknown, types of antibodies.[7] Although it remains unclear whether there is a causal link between anti-FGFR3 antibodies and lung adenocarcinoma, or whether the presence of antibodies reflects dysimmune SN related to sarcoidosis, the case presented here raises the possibility of an association between both conditions.

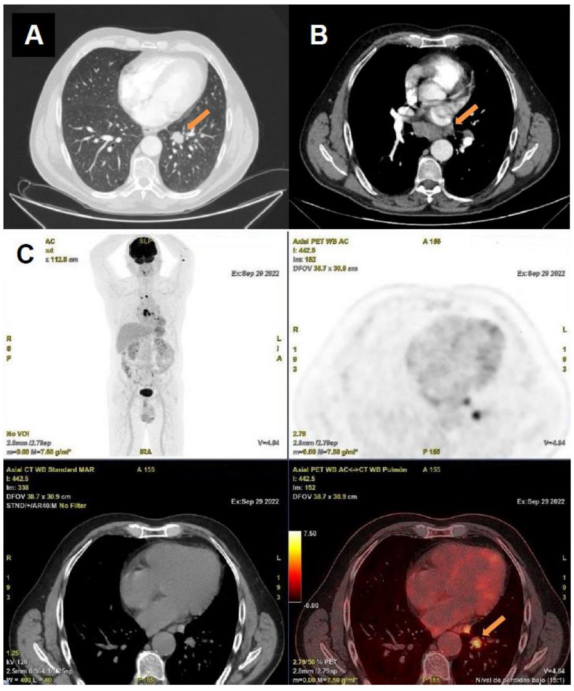

Figure 2 Staging imaging study conducted as part of the diagnostic workup performed to rule out an occult neoplasm. The chest CT scan (A) reveals a pulmonary nodule measuring 21 mm in its largest diameter, located in the left lower lobe, as well as bilateral prevascular (largest measuring 12 mm), infracarinal (largest measuring 21 mm), and hilar adenopathies (largest measuring 17 mm) located on the right side (B). The PET-CT scan (C) revealed hypermetabolism in the pulmonary nodule and the mediastinal adenopathies.

CRediT authorship contribution statement

All authors provided intellectual content to this study and approved the final version of the manuscript.

Ethical considerations

Patient confidentiality was preserved. The patient gave verbal and written informed consent for the publication of this case report.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgements

We would like to express our sincerest gratitude to the neurophysiology, radiodiagnosis, and nuclear medicine departments of Hospital Universitario de Cruces for their constant and willing collaboration with the neurology department, and particularly in this case for the images and complementary test results.

References

1. Kuntzer T, Antoine JC, Steck AJ. Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies). Muscle Nerve. 2004;30(3):255—68, http://dx.doi.org/10.1002/mus.20100.
2. Amato AA, Ropper AH. Sensory ganglionopathy. N Engl J Med. 2020;383:1657—62, http://dx.doi.org/10.1056/NEJMra2023935.
3. Antoine JC. Sensory neuronopathies, diagnostic criteria and causes. Curr Opin Neurol. 2022;35(5):553—61, http://dx.doi.org/10.1097/WCO.0000000000001105.
4. Ubirajara García R, Gama Ricardo JA, Abreu Horta C, García Garibaldi S, Nucci A, França MC Jr. Ulnar sensory-motor amplitude ratio: a new tool to differentiate ganglionopathy from polyneuropathy. Arq Neuropsiquiatr. 2013;71(7):465—9, http://dx.doi.org/10.1590/0004-282X20130063.
5. Fargeot G, Echaniz-Laguna A. Sensory neuronopathies: new genes, new antibodies and new concepts. J Neurol Neurosurg Psychiatry. 2021;92:398—406, http://dx.doi.org/10.1136/jnnp-2020-325536.
6. 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, http://dx.doi.org/10.1212/NXI.0000000000001014.
7. Antoine JC, Camdessanché JP. Paraneoplastic neuropathies. Curr Opin Neurol. 2017;30(5):513—20, http://dx.doi.org/10.1097/WCO.0000000000000475.
8. Gwathmey KG. Sensory neuronopathies. Muscle Nerve. 2016;53(1):8—19, http://dx.doi.org/10.1002/MUS.24943.
9. Camdessanché J-P, Jousserand G, Franques J, Pouget J, Delmont E, Créange A, et al. A clinical pattern-based etiological diagnostic strategy for sensory neuronopathies: a French Collaborative study. J Peripher Nerv Syst. 2012;17:331—40, http://dx.doi.org/10.1111/J.1529-8027.2012.00411.X.
10. Gavrilova N, Starshinova A, Zinchenko Y, Kudlay D, Shapkina V, Malkova A, et al. Small fiber neuropathy in sarcoidosis. Pathophysiology. 2021;28(4):544—50, http://dx.doi.org/10.3390/pathophysiology28040035.
11. Antoine JC, Boutahar N, Lassablière F, Reynaud E, Ferraud K, Rogemond V, et al. Antifibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy. J Neurol Neurosurg Psychiatry. 2015;86:1347—55, http://dx.doi.org/10.1136/JNNP-2014-309730.
12. Moritz CP, Tholance Y, Vallayer PB, Do LD, Muñiz-Castrillo S, Rogemond V, et al. Anti-AGO1 antibodies identify a subset of autoimmune sensory neuronopathy. Neurol Neuroimmunol Neuroinflamm. 2023;10(3):e200105, http://dx.doi.org/10.1212/NXI.0000000000200105.
13. Tholance Y, Moritz CP, Rosier C, Ferraud K, Lassablière F, Reynaud-Federspiel E, et al. Clinical characterisation of sensory neuropathy with anti-FGFR3 autoantibodies. J Neurol Neurosurg Psychiatry. 2020;91:49—57, http://dx.doi.org/10.1136/JNNP-2019-321849.

L. Fernández-Llarena*, A. Moreno-Estébanez, A. González-Eizaguirre, A. Jauregi-Barrutia

Servicio de Neurología, Hospital Universitario de Cruces, Barakaldo, Spain

* Corresponding author.
E-mail address: leirefernandezllarena@gmail.com (L. Fernández-Llarena).

https://doi.org/10.1016/j.nrleng.2025.09.001
2173-5808/ © 2024 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Bilateral hack sign not necessarily implies paraparesis

No hay señal de hackeo bilateral implica necesariamente paraparesia

Dear Editor,

We read with interest the article by González Martín et al.[1] about a 50-year-old man with partial rupture of the right quadriceps tendon and complete rupture of the left quadriceps tendon after a thoraco-lumbar trauma due to an accidental fall from a height of approximately 2 m. Immediately after the trauma, the patient reported paraparesis and was unable to walk. Work-up by traumatologists was non-informative. Three weeks after the trauma, bilateral hack sign was observed and the patient was diagnosed with (partial) rupture of the quadriceps tendon. He underwent tendon repair, with a favourable outcome. The study is interesting, but raises concerns that should be discussed.

There is a discrepancy between the clinical neurological examination revealing weakness (MRC 4+) for knee extension and hip flexion on the right side (partial rupture of the quadriceps tendon) and normal muscle strength (MRC 5) for left knee extension and hip flexion, and the diagnosis of paraparesis.[1] As, according to the description of the neurological examination, there was no muscle weakness in the left lower limb, the diagnosis of paraparesis is not comprehensible.

There is also a discrepancy between the neurological examination showing normal knee extension on the left side and total quadriceps tendon rupture on the left side. In the event of quadriceps tendon rupture, a patient should not be able to extend his knee. It should be clarified if surgeons truly found total rupture during inspection of the site.

Furthermore, a patient with only mild weakness on flexion and knee extension on one side should be able to stand and walk. Since only incomplete rupture of the quadriceps tendon was observed on the right side, the patient should have been able to stand, at least on the right leg. This discrepancy should also be addressed.

A limitation of the study is that the authors do not mention whether the patient underwent tendon repair on the left side only or bilaterally. Complete rupture of the quadriceps tendon requires surgical intervention, whereas incomplete rupture is usually treated conservatively. As the patient had incomplete rupture of the right quadriceps tendon, it is very likely that surgery was carried out only on the left side. However, this uncertainty requires clarification.

It is also unclear why it took 3 weeks, during which the patient was unable to stand or walk, before comprehensive diagnostic work-up was initiated. An alert patient with preserved cognitive and intellectual abilities should attend hospital earlier. Did the patient present cognitive impairment?

Overall, this interesting study has limitations that call the results and their interpretation into question. Addressing these limitations could further strengthen and reinforce the statement of the study. Paraparesis can be diagnosed only if there is weakness in both limbs, mild proximal weakness of one leg should not prevent the patient from standing, and rupture of a quadriceps tendon should not be associated with normal knee extension.

CRediT authorship contribution statement

JF: design, literature search, discussion, first draft, critical comments, final approval; FS and A-CA: literature search, discussion, critical comments, final approval.

Ethical approval

The study was conducted in accordance with ethical guidelines. The study was approved by the institutional review board.

Consent to participate

Consent to participate was obtained from the patient.

Consent for publication

Consent for publication was obtained from the patient.

Funding

No funding was received.

Conflicts of interest

None declared.

Data availability

All data are available from the corresponding author.