Case Report

# Anti-Zic4 paraneoplastic cerebellar degeneration in a patient with EGFR-mutated NSCLC: a case report

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**Abstract:** Paraneoplastic cerebellar degeneration (PCD) is one of the most prevalent neurological paraneoplastic syndromes, typically associated with small cell lung cancer (SCLC). PCD is thought to be caused by proteins expressed by tumor cells which trigger an antibody-mediated immune response. Despite PCD being commonly associated with anti-Yo, anti-Hu and anti-Tr/DNER antibodies, PCD is the most prevalent paraneoplastic syndrome in patients harboring anti-Zic4 antibodies. We report what, to our knowledge, is the first known case of anti-Zic4 mediated PCD in a patient with *EGFR*-mutated metastatic non-small cell lung cancer (NSCLC). Our patient was in complete response (CR) to targeted therapy and presented to the emergency room with drowsiness, unsteady gait and memory lapses. The diagnostic work-up revealed a diffuse cerebellar atrophy in the MRI, ruling out brain metastasis and leptomeningeal carcinomatosis. A body-CT scan showed no signs of recurrent disease. The cerebrospinal fluid (CSF) was within normal parameters. An onconeural antibody panel was conducted in a peripheral blood sample, detecting high levels of anti-Zic4 antibody by indirect immunofluorescence (IFI), results later confirmed by immunoblot testing. With the suspected diagnosis of an anti-Zic4 PCD, the case was discussed with the neurology department and treatment with high dose methylprednisolone was initiated. Considering the lack of substantial clinical benefit, the patient was then treated with intravenous immunoglobulins (IVIG) for 5 days, showing modest improvement. At this time, the patient presented minor disease relapse in the form of a sub-centimetric pulmonary nodule. Despite one cycle of chemotherapy, the patient's neurological condition deteriorated leading to fatal pneumonia secondary to progressive dysphagia. There is scarce evidence of paraneoplastic syndromes in *EGFR*-mutated NSCLC. Further research is warranted to stablish a possible association between anti-Zic4 and the EGFR molecular pathway.

**Keywords:** Paraneoplastic cerebellar degeneration (PCD); anti-Zic4 antibodies; EGFR; non-small cell lung cancer (NSCLC); case report

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## Introduction

Non-small cell lung cancer (NSCLC) is the most frequent histological subtype of lung malignant tumours and remains a major cause of cancer-related death worldwide.

The therapeutic management of metastatic NSCLC has been recently transformed by the discovery of several actionable driver mutations and the approbation of successful therapies against an increasing number of molecular targets.

In particular, the development of successive generations of tyrosine-kinase inhibitors against the sensitizing mutations on *EGFR*, highlighting the approbation of osimertinib as the first-line treatment for *EGFR*-mutated NSCLC, has changed the therapeutic scenery of these patients. Nevertheless, a better knowledge of the mechanisms of resistance and the finding of new therapeutic strategies after failure of frontline osimertinib currently remain a major challenge.

Paraneoplastic neurological syndromes are rare clinical disorders which arise from an inappropriate cross-reaction between host cells of the central nervous system (CNS) and immunologically targeted malignant cells. Their clinical manifestations are diverse, and their diagnosis may be challenging, particularly since they usually precede the diagnosis of malignancy.

Despite their well-established association with small-cell lung cancer, there is scarce evidence of paraneoplastic syndromes in NSCLC with *driver* mutations. Further research is needed for a proper understanding of the pathogenic mechanisms underlying paraneoplastic neurologic disease, particularly in association with *EGFR*-mutated lung cancer. We present the following article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-989/rc).

## Case presentation

We present the case of a 57 years-old patient with a metastatic lung adenocarcinoma, stage IVa (cT2aN0M1a) due to bilateral pulmonary nodules and lymphangitis carcinomatosis. A molecular testing of the tumour at diagnosis found an *EGFR* exon 19 deletion (E19del) by polymerase chain-reaction (PCR kit Cobas), so the patient started first line of systemic therapy with afatinib 40 mg/24 h in April 2016, reaching partial response in subsequent CT scans.

In November 2017, a progression of disease was confirmed in the lungs and pleura, with no clinical or radiological signs of dissemination to the CNS. A new lung biopsy confirmed the presence of the T790M mutation in exon 20 of *EGFR*, with persistence of exon 19 deletion. At this point, the patient was enrolled in a clinical trial with osimertinib 80 mg/day and a JAK-2 inhibitor, achieving CR by body CT scan at first follow-up.

More than 2 years later, in May 2020, the patient presented to the hospital with a three weeks progressive course of drowsiness [Glasgow Coma Scale (GCS) 14/15], intentional tremor, unsteady gait and frequent memory lapses. Neurological examination showed bilateral intentional tremor in the finger-to-nose and heel-to-knee tests, bilateral dysdiadochokinesia, dysarthria, and positive Stewart-Holmes maneuver.

Routine blood test, hormone profile and a body and brain CT-scan showed no alterations, with persistent CR. The cerebrospinal fluid (CSF) analysis found no relevant alterations (leucocytes 1 cell/mm$^3$, glycorrhachia 57 mg/dL, proteins 56 mg/dL, negative Gram stain and cultures).

A brain MRI revealed a cortico-subcortical atrophy of the brain stem, loss of cerebellum volume and enlargement of the cerebellar cisternae, 4th ventricle and cisterna magna, as well as prominence of the cerebellar folia, all suggestive of diffuse cerebellar atrophy. There was no evidence of CNS metastasis or leptomeningeal carcinomatosis (*Figure 1*). These findings posed a differential diagnosis including toxic encephalopathy, multisystemic atrophy and paraneoplastic syndromes.

Onconeural antibodies were tested in a peripheral blood sample, finding high levels of anti-Zic4 antibody by indirect immunofluorescence (IFI) and immunoblot testing (Euroimmun) (*Figures 2*,*3*). With the suspected diagnosis of anti-Zic4 induced paraneoplastic cerebellar degeneration (PCD), treatment with high-dose methylprednisolone (1 g/day for 5 days) was started, without clinical improvement.

Intravenous immunoglobulins (IVIG) were then administered (0.4 g/kg/day for 5 days), showing a modest clinical benefit consisting of a mild improvement of the tremor and somnolence. However, the cognitive sequelae (Mini-Mental State Examination of 21 and anterograde amnesia) and the unsteady gait persisted.

The patient remained on treatment in the clinical trial throughout that time, except during the administration of IVIG, considering that the clinical condition probably had a paraneoplastic origin and was not related to treatment

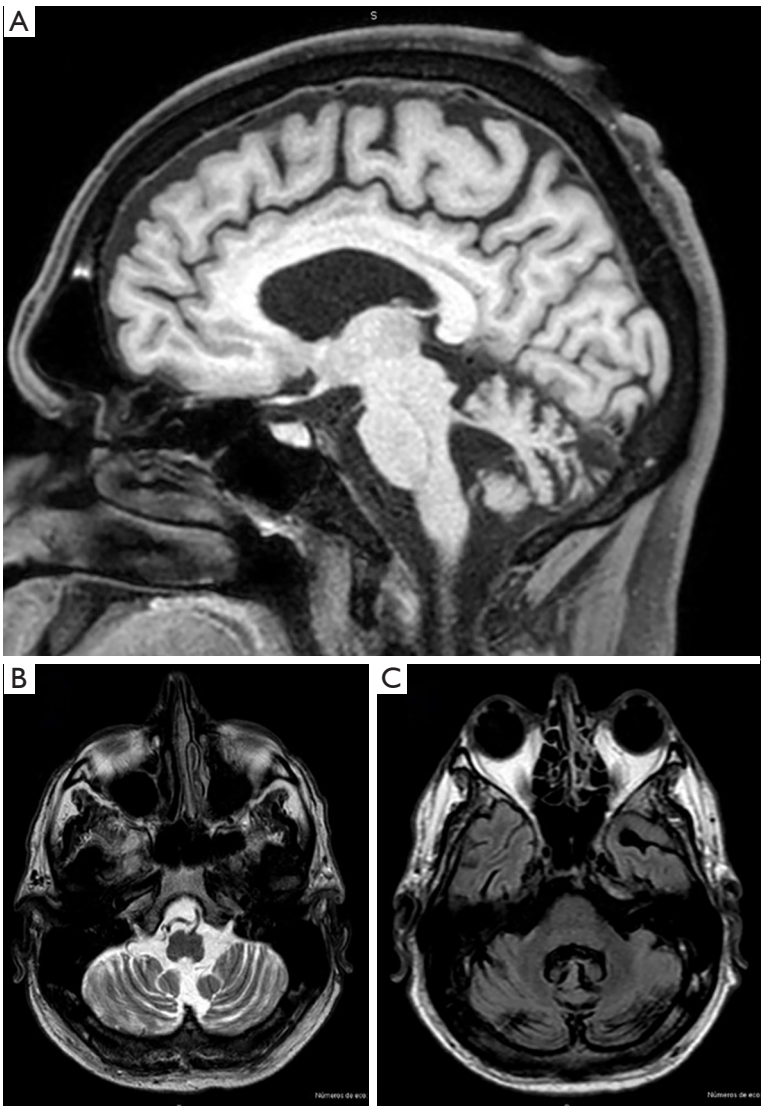
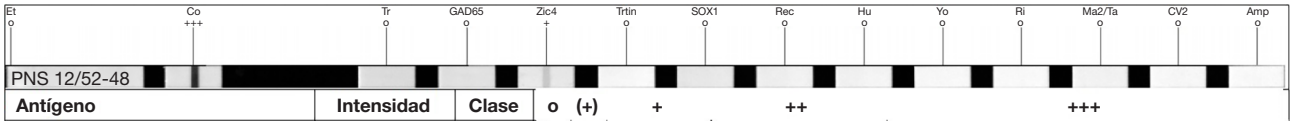



**Figure 1** Brain MRI showing cerebellum atrophy and retraction of cerebellar folia in sagittal view with T1 sequence (A) and axial view with FLAIR (B) and T2 sequence (C). FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.

toxicity. In August 2020, a follow-up body CT scan and brain MRI confirmed persistent CR.

In the subsequent CT scan in October 2020, a 9-mm pulmonary nodule is described with a SUVmax of 3.2 in the PET-CT scan, which did not reveal other metabolically active lesions. The case was discussed in the multidisciplinary board. A tissular biopsy was considered infeasible because of the small size of the nodule and difficult accessibility. However, considering the progressive worsening of the neurological symptoms, this radiologic finding was assumed as a progression of disease. Therefore, third line of systemic therapy was proposed, and the patient started standard chemotherapy treatment for lung adenocarcinoma.

After the first cycle of chemotherapy in December 2020, the patient experienced a rapid worsening of the paraneoplastic syndrome, consisting of severe somnolence, dysarthria and ataxia. A possible underlying mechanism could be an increased onconeural antigen release following disease response to treatment. The case was discussed again in the multidisciplinary board along with the neurology colleagues, deciding a new course of IVIG (2 g/kg/day for 5 days), with no clinical improvement. In a chest CT scan performed in January 2021 in the context of an acute pulmonary embolism, the pulmonary nodule was stable and




| Antígeno | Intensidad | Clase |
|---|---|---|
| Amphiphysin (Amp) | 2 | o |
| CV2 (CV2) | 2 | o |
| PNMA2/Ta (Ma2/Ta) | 0 | o |
| Ri (Ri) | 2 | o |
| Yo (Yo) | 1 | o |
| Hu (Hu) | 3 | o |
| Recoverin (Rec) | 3 | o |
| SOX1 (SOX1) | 2 | o |
| Titin (Titin) | 2 | o |
| Zic4 (Zic4) | 31 | + |
| GAD65 (GAD65) | 2 | o |
| Tr (DNER) (Tr) | 1 | o |
| Control (Co) | 155 | +++ |

**Figure 2** Western blot analysis revealing a positive band corresponding to anti-Zic4 antibodies. The signal intensity of the band (Zic4, +) is directly proportional to the serum concentration of Zic4 protein. Grading of band intensities for different antibodies is represented as "+/++/+++" relative to a control "Co, +++".

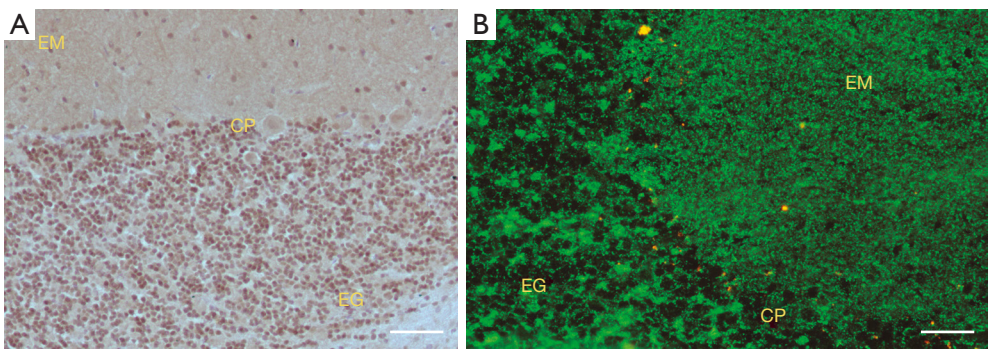



**Figure 3** Immunohistochemistry (A) and indirect immunofluorescence (B) showing staining of the nuclei mainly in the granular layer of the cerebellum. CP and neurons of the molecular layer reveal a lower intensity staining. Scale bar: 40 µm. EM, molecular layer; CP, Purkinje cells; EG, granular layer.

there was no evidence of tumoral disease at any other level.

The rapid neurological deterioration impeded our patient to receive further active treatment, prioritizing symptomatic control with the home palliative care team. He experienced progressive dysphagia with oral intolerance leading to fatal aspiration bronchopneumonia. A timeline with the most relevant events of the case is presented in *Figure 4*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Discussion

This is to our knowledge the first report of anti-Zic4 PCD in *EGFR*-mutated NSCLC, as well as the first time a paraneoplastic syndrome associated with isolated anti-Zic-4 antibodies is communicated in NSCLC.

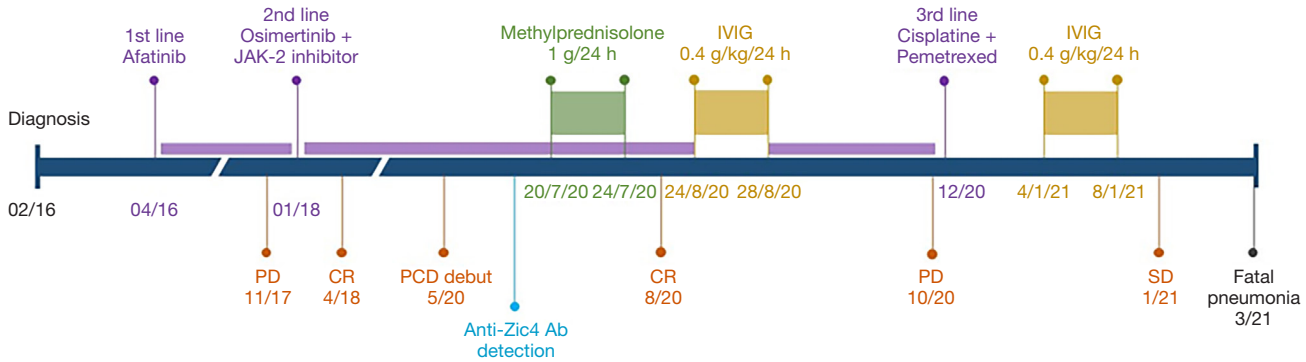



**Figure 4** Chronological timeline. The figure represents the most important events of the case. PD, progression disease; CR, complete response; PCD, paraneoplastic cerebellar degeneration; IVIG, intravenous immunoglobulins; SD, stable disease.

Despite being an uncommon disorder (incidence <1/10,000 cancer patients), PCD is one of the most prevalent paraneoplastic neurologic syndromes, being preferentially associated with lung cancer [particularly small cell lung cancer (SCLC)], gynecologic and breast cancer and Hodgkin lymphoma, preceding tumour diagnosis in more than 50% of the patients (1).

Many paraneoplastic syndromes are immune-mediated and it seems they can be triggered when tumours express proteins that are normally restricted to immune privileged neurons. This generates an immune response through onconeural antibodies that can be detected both in peripheral blood and CSF (2).

The *ZIC* gene family encode for zinc-proteins that play an important role in CNS development. Anti-Zic4 are directed against the zinc-finger domain of the intracellular transcription factor Zic4 (3).

Although PCD is usually linked to anti-Yo, anti-Hu and anti-Tr/DNER, it has been recently associated with other antibodies, including anti-Zic4 (4). In fact, PCD is the most common syndrome in patients harbouring anti-Zic4 antibodies and up to 92% of the cases are associated with SCLC (5). However, anti-Zic4 tend to express along with other antibodies such as anti-Hu or anti-CRMP5, hence showing a wider spectrum of neurological symptoms. Therefore, the clinical significance of anti-Zic4 is still unclear.

Up to date, 15 cases of paraneoplastic syndromes associated with isolated anti-Zic-4 have been reported (6), presenting most of them (13/15) with PCD, one with subacute sensory neuropathy and one with Lambert-Eaton syndrome.

Upfront immunosuppressive treatment was the elective therapeutic approach. Nonetheless, PCD has a poor outcome, in particular when associated with antibodies directed against intracellular antigens as is Zic4. In this review, out of 5 patients with treatment data, two had no response, two improved somewhat with persisting symptoms and only one achieved complete clinical remission.

There is scant evidence of paraneoplastic syndromes in *EGFR* mutated NSCLC. After a thorough research in the literature, we only found one case of dermatomyositis in a patient with an *EGFR* exon 20 insertion mutation (7).

No association between anti-Zic4 and the *EGFR* molecular pathway has been described up to date, hence further research is needed.

The impossibility to obtain a new biopsy at disease progression is a limitation in our case, since we can not completely rule out the possibility of a transformation to SCLC, which is a frequent known mechanism of acquired resistance to *EGFR* TKIs, as well as the histology more commonly associated with anti-Zic4 antibodies. Notwithstanding, the rather indolent course of the tumour, with a sole sub-centimetre pulmonary nodule, a low FDG-PET uptake and no evidence of disease progression at any other location, makes SCLC transformation unlikely to be the underlying process in this case.

Taking into account that the onset of a paraneoplastic syndrome may entail disease progression even if it is not detectable by standard radiological techniques, the use of liquid biopsy should be considered for patients with known NSCLC in CR when a paraneoplastic syndrome is suspected.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-989/rc

*Peer Review File:* Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-989/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-989/coif). PG declares personal financial interests as advisor for AbbVie, AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, Bristol, Gilead, Guardant Health, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Rovi, Sysmex and Takeda. TAG declares personal financial interests as advisor for IPSEN, Roche, Pfizer, Sanofi, Bayer, Astellas, Jansen-Cilag, BMS, Merck, EISAI, MSD. JMC declares personal financial interests as advisor for IPSEN, Roche, Pfizer, Sanofi, Astellas, Jansen-Cilag, BMS, EISAI, MSD. The other authors have no conflicts of Interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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