ramr
American Review of Respiratory Medicine
Revista Americana de Medicina Respiratoria

CASE REPORT

ISSN 1852-236X

Paraneoplastic Cerebellar Degeneration Revealing Lung Cancer

Degeneración cerebelosa paraneoplásica reveladora del cáncer de pulmón

Adil, Zegmout[1]; Hanane, Asri[2]; Anis, Rafik[2]; Ahmed, Zahir Lakhal[3]; Hicham, Souhi[2]; Hanane, El Ouazzani[2]; Ismail, Abderrahmane, Rhorfi[2]

Received: 05/26/2024
Accepted: 10/23/2024

Correspondence
Adil Zegmout. E-mail:
adilzgmt@gmail.com

ABSTRACT

Paraneoplastic cerebellar degeneration is a rare neurological syndrome characterized by the acute or subacute onset of neurological symptoms associated with cancer. The prognosis is often poor. We report the case of a 55-year-old patient with small cell lung carcinoma revealed by paraneoplastic cerebellar degeneration. Our case is notable for the significant improvement in the neurological status following tumor treatment, suggesting that neurological symptoms may regress in response to targeted therapies for chemosensitive tumors such as small cell lung carcinomas.

Key words: Paraneoplastic cerebellar degeneration; Small cell lung carcinoma; Prognosis

RESUMEN

La degeneración cerebelosa paraneoplásica es un síndrome neurológico raro, definido por la aparición aguda o subaguda de un síndrome neurológico asociado con cáncer. El pronóstico suele ser muy desfavorable. Presentamos el caso de un paciente de 55 años con un carcinoma bronquial de células pequeñas revelado por una degeneración cerebelosa paraneoplásica. Lo notable en nuestro caso es la mejoría significativa del estado neurológico posterior al tratamiento del tumor, lo que sugiere la posibilidad de una reversión de los síntomas neurológicos en respuesta a terapias dirigidas a tumores quimio-sensibles, como los carcinomas bronquiales de células pequeñas.

Palabras clave: Degeneración cerebelosa paraneoplásica; Carcinoma bronquial de células pequeñas; Pronóstico

INTRODUCTION

Paraneoplastic cerebellar degeneration (PCD) refers to the acute or subacute onset of neurological symptoms associated with cancer(1). It is a rare condition whose incidence and prevalence are still unclear (2). In most cases, neurological disorders precede the discovery of the primary tumor.

Despite the aggressive treatments targeting the underlying cancer, the neurological prognosis for paraneoplastic syndromes such as PCD is generally poor, especially in cases mediated by onconeural antibodies (3). However, in our case, chemotherapy led to rapid clinical improvement, which is an unusual response in most paraneoplastic syndromes and highlights the particularity of this case.

Rev Am Med Resp 2024;24:189-193
https://doi.org./10.56538/ramr.HQLK9171

[1] Faculty of Medicine and Pharmacy of Casablanca, Morocco; Pulmonology Service, Hospital Militar Mohammed V, Rabat, Morocco
[2] Pulmonology Service, Hospital Militar Mohammed V, Rabat, Morocco.
[3] King Fahd School of Translation, Tanger, Morocco.

It is well known that small cell lung carcinoma (SCLC) exhibits a remarkable initial sensitivity to chemotherapy, resulting in a significant reduction of tumor masses. This sensitivity might be related to the clinical improvement observed in our patient, although further confirmation is needed.

CASE REPORT

We present the case of a 55-year-old patient with a history of gait instability that had manifested over the course of a year, with gradual worsening of his condition. The neurological examination showed dysarthria along with ataxic gait and increased base of support, as well as dysmetria and bilateral and symmetrical adiadochokinesia in all four limbs. These clinical symptoms occurred in a chronic smoker, asymptomatic at the respiratory level and with a preserved general status. The initial brain magnetic resonance imaging did not reveal any abnormalities, ruling out the presence of a tumor process. Vitamin E and B12 levels, as well as thyroid hormones, were within normal ranges. Additionally, the results of the immunological analysis were negative. However, a specific search for onconeural antibodies revealed the presence of positive anti-Hu antibodies.

A chest CT scan showed a pulmonary lesion in the lower right lobe (at the nelson level) with irregular contours that enhanced after contrast injection, measuring 41x29x53 mm (transverse x anteroposterior x height) and multiple mediastinal adenopathies in chains 4R and 6. (figure 1-A). Although the bronchoscopy was normal, CT-guided lung biopsies revealed small-cell lung cancer (Figure 2).

The combination of a suggestive clinical presentation chronologically associated with lung cancer, along with the presence of anti-Hu antibodies led to the diagnosis of PCD. The positron emission tomography (PET) revealed a hypermetabolic pulmonary parenchymal mass in the right nelson region, without pathological nodal hypermetabolism at the mediastinal level or other suspicious hypermetabolic foci in the remaining structures explored (Figure 1-B).

The patient received combined chemotherapy and radiotherapy concurrently. Chemotherapy was administered in 3-week cycles with cisplatin (75-80 mg/m² i.v. on day 1) and etoposide (100-120 mg/m² i.v. on days 1-3), completing 4 cycles. Simultaneously, the patient underwent thoracic radiotherapy with a protocol of 45 Gy, fractionated into 1.5 Gy per session, twice daily for 3 weeks. The post-treatment evaluation after four chemotherapy cycles showed a reduction in tumor size (Figure 1-C), accompanied by a significant improvement in the patient's neurological status: his gait became more stable, and he was able to maintain his autonomy with a good quality of life. The patient subsequently received prophylactic cranial radiotherapy.

DISCUSSION

Paraneoplastic neurological syndromes (PNSs) are neurological manifestations associated with cancer that can't be explained neither by the invasion of the nervous system by tumor cells nor by iatrogenic, metabolic, infectious, or nutritional causes. They can affect the central or peripheral nervous systems, as well as the neuromuscular junction (2). These are rare conditions that precede the discovery of cancer in about 65% of cases (1) and their incidence and prevalence remain largely unknown; PCD is estimated to occur in 2 out of every 1000 cases (3). However, most estimates come from referral centers rather than epidemiological studies. Over a ten-year period, an European consortium of 11 countries identified only 900 patients with

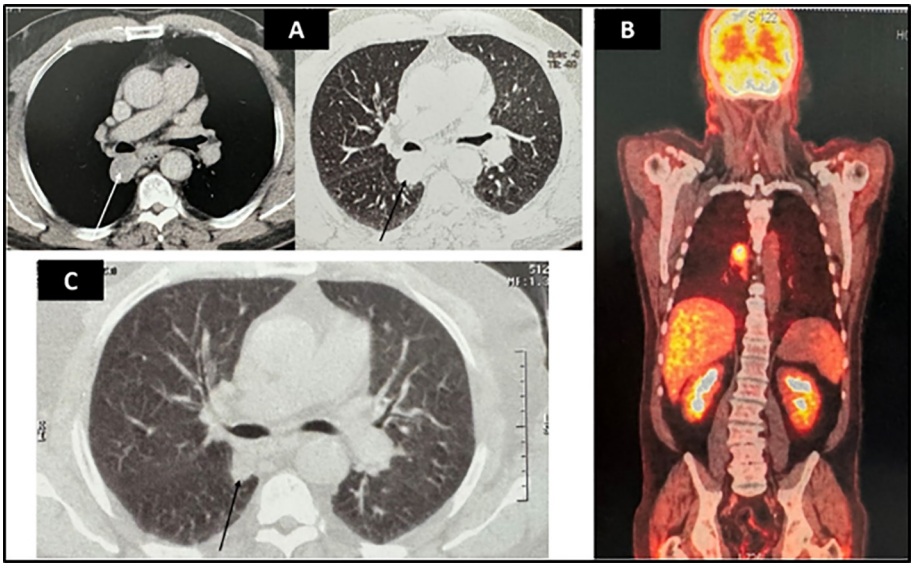

Figure 1. A) The computed tomography (CT) of the chest in mediastinal and parenchymal sections revealed the presence of a pulmonary lesion in the right lower lobe (arrows). B) The positron emission tomography (PET) revealed a hypermetabolic pulmonary parenchymal mass in the right nelson region, without suspicious pathological hypermetabolism in the remaining structures explored. C) The follow-up computed tomography shows a regression of the tumor mass (arrow).

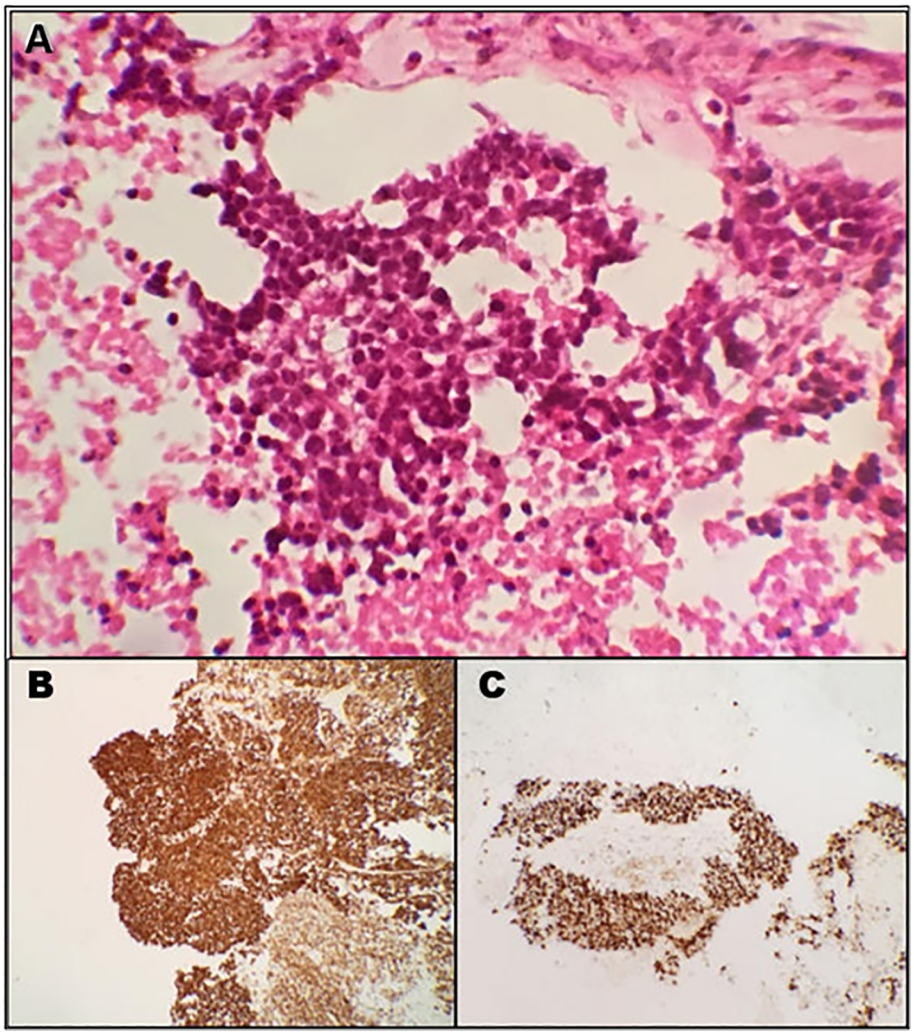

Figure 2. Histological study. A) Poorly differentiated tumor proliferation, featuring nests of small basophilic tumor cells with dark hyperchromatic nuclei (ET GX400). B) Expression of synaptophysin by tumor cells. C) High Ki67 proliferation index.

PNS (2). PCD can affect both men and women, and the distribution of cases between genders may vary depending on the type of associated tumor.

The physiopathology of PCD is not fully established, but it seems that some autoantibodies directed against tumor cells could interact with the cells of the nervous system (4). Over the past 20 years, the identification of onconeural antibodies has marked a significant advancement that supports the hypothesis of an autoimmune mechanism. Their presence suggests the paraneoplastic nature of the neurological condition and guides the cancer search based on the type of antibody identified. SCLC is a neuroendocrine variety. These neoplasms are associated with neuroendocrine differentiation, characterized by the expression of specific markers such as achaete-scute homologue 1 (Ascl1) and insulinoma-associated protein 1 (INSM1), which play a key role in the biology and pathology of neuroendocrine cells. Additionally, it has been demonstrated that a subgroup of these tumors exhibits humoral activity, which may explain some clinical manifestations due to the release of neuroendocrine amines into the bloodstream, such as arginine vasopressin or gastrin releasing peptide (5,6). PCD is commonly associated with anti-Yo antibodies in women with malignant ovarian tumors (7) and with anti-Tr antibodies in patients with Hodgkin's lymphoma (8). Patients with small cell lung cancer can develop several immune responses associated with PCD. In this context, up to 41% of patients develop anti-VGCC

antibodies, 23% develop anti-Hu antibodies, and a minority develop other antibodies such as anti-PCA2, anti-Ri, anti-mGluR1, anti-Zic4, anti-Ma, anti-CV2/CRMP5, and anti-ANNA3 antibodies (9). These antibodies may be present in both serum and cerebrospinal fluid.

While SCLC is frequently associated with PNS, it is not the only type of tumor responsible for these syndromes. Tumors such as breast carcinoma or lymphomas can also induce PNS. Additionally, even though the treatment of the underlying tumor can improve the symptoms, in many cases –especially when the antibodies involved are intracellular– the systemic symptoms may persist despite tumor remission.

PCD can often precede the onset of cancer by a few months, or even one to two years. Its onset is usually subacute but can sometimes be more acute. Typically, symptoms appear over the course of a few weeks or months, but in some cases, they may emerge within days or even hours, in a pseudo-vascular manner. Typical clinical symptoms include a bilateral static and kinetic cerebellar syndrome, with dysarthria, vertigo, and nystagmus also being observed (9). Brain imaging may initially appear normal, but after several months of progression, cerebellar atrophy with dilation of the fourth ventricle may become evident, without involvement of the brainstem.

The diagnosis of PNS is classified as definite, probable, or possible, based on criteria that assess the level of certainty linking the observed neurological disorder to a known or suspected tumor(10). Establishing the relationship between suggestive neurological symptoms and the presence of onconeural antibodies or evidence of an underlying cancer is crucial. Approximately 50% of the cases do not present identifiable onconeural antibodies. So, the absence of these onconeural antibodies does not rule out a PNS diagnosis. In such cases, the diagnosis of PNS is based on the association of suggestive clinical signs that are chronologically related to a cancer, as observed in our case.

The treatment of PCD primarily focuses on treating the primary tumor, which is essential, especially in paraneoplastic syndromes associated with an antibody targeting a membrane antigen. However, if there is no response to tumor treatment, immunosuppressive options may be considered. Corticosteroids, high-dose intravenous human immunoglobulin, plasma exchanges, tacrolimus, and more recently rituximab have been used, although their efficacy is often limited in PNS, particularly those of central origin, mostly when the antigen is intracellular rather than membrane-bound (11).

The neurological prognosis for patients with PCD remains unfavorable even after radical treatment of the underlying tumor. The persistence of these symptoms has a negative impact on the quality of life of the patients. In fact, less than 10% of them are able to walk unaided. Additionally, a median survival time of just 22 months has been reported (12). In our patient's case, early diagnosis of PCD enabled the identification of a localized-stage small cell lung carcinoma. This early detection provided the patient with the best possible treatment opportunity, despite the guarded prognosis typically associated with this histological type of cancer. Notably, our observation stands out due to the improvement in the patient's neurological condition following tumor treatment. This case suggests that neurological symptoms of PCD may improve in patients with small cell carcinoma due to the high sensitivity of these tumors to chemotherapy, which allows for a significant reduction in tumor burden and, consequently, a potential improvement in clinical manifestations.

CONCLUSION

The presented case highlights the importance of considering SCLC in patients with atypical neurological symptoms, such as those observed in PCD. Notably, in this case, there was a significant neurological improvement following tumor treatment, suggesting that, in certain cases, paraneoplastic symptoms may respond favorably to targeted oncological treatment, especially when the neoplasm is sensitive to chemotherapy. This case underscores the importance of early diagnosis and appropriate treatment in the progression of PNSs associated with chemosensitive tumors like SCLC.

Conflict of interest
Authors have no conflicts of interest to declare.

REFERENCES

1. Didelot A, Honnorat J. Les syndromes neurologiques paranéoplasiques [Paraneoplastic neurological syndromes]. Rev Med Interne. 2011;32:605-11. French. https://doi.org/10.1016/j.revmed.2010.09.007.

2. Rosencher L, Maisonobe T, Lavole A, Milleron B, Ferroir JP. Syndrome neurologique paranéoplasique à anticorps anti-CV2/CRMP5 révélateur d'un cancer bronchique à petites cellules. Efficacité du traitement du cancer bronchique [Neurologic paraneoplastic syndrome with anti-CV2/CRMP5 antibodies revealing a small cell lung cancer. Effectiveness of the lung cancer treatment]. Rev Neurol (Paris). 2012;168:371-4. French. https://doi.org/10.1016/j.neurol.2011.07.016.
3. Graus F, Dalmau J. Paraneoplastic neurological syndromes: diagnosis and treatment. Curr Opin Neurol. 2007;20:732-7. https://doi.org/10.1097/WCO.0b013e3282f189dc.
4. Chaabane K, Turki E, Zouari F, Charfi S, Guermazi M, Mhiri C. Dégénérescence cérébelleuse paranéoplasique révélant un cancer du sein : à propos d'un cas [Paraneoplastic cerebellar degeneration as the presenting manifestation of breast carcinoma: a case report]. Rev Med Interne. 2013;34:713-5. French. https://doi.org/10.1016/j.revmed.2013.02.005.
5. Coulson JM, Stanley J, Staff D, Woll PJ. 599 Evaluation of vasopressin (AVP) and VIIa receptor expression in SCLC cell lines: Potential for an autocrine growth loop? Lung Cancer. 1997;Supplement 1(18):154.
6. Ito T, Kudoh S, Fujino K, Sanada M, et al. Pulmonary Neuroendocrine Cells and Small Cell Lung Carcinoma: Immunohistochemical Study Focusing on Mechanisms of Neuroendocrine Differentiation. Acta Histochem Cytochem. 2022;55:75-83. https://doi.org/10.1267/ahc.22-00031.
7. Rojas I, Graus F, Keime-Guibert F, et al. Long-term clinical outcome of paraneoplastic cerebellar degeneration and anti-Yo antibodies. Neurology. 2000;55:713-5. https://doi.org/10.1212/wnl.55.5.713.
8. Bernal F, Shams'ili S, Rojas I, et al. Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin's disease. Neurology. 2003;60:230-4. https://doi.org/10.1212/01.wnl.0000041495.87539.98.
9. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. The Lancet Neurology. 2008;7:327-40. https://doi.org/10.1016/S1474-4422(08)70060-7
10. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004;75:1135-40. https://doi.org/10.1136/jnnp.2003.034447.
11. Esposito M, Penza P, Orefice G, Pagano A, Parente E, Abbadessa A, Bonavita V. Successful treatment of paraneoplastic cerebellar degeneration with Rituximab. J Neurooncol. 2008;86:363-4. https://doi.org/10.1007/s11060-007-9479-z.
12. Giometto B, Grisold W, Vitaliani R, Graus F, Honnorat J, Bertolini G; PNS Euronetwork. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol. 2010;67:330-5. https://doi.org/10.1001/archneurol.2009.341.