Journal of the Neurological Sciences 396 (2019) 184–186

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Long–Standing evolution of paraneoplastic cerebellar degeneration in a diffuse large B-cell lymphoma

ARTICLE INFO

Keywords:
Cerebellar degeneration
Diffuse large B-cell lymphoma
Marginal-zone B-cell lymphoma

Paraneoplastic cerebellar degeneration (PCD) is characterized by pancerebellar ataxia with diplopia, nystagmus and dysarthria that might evolve subacutely or over months to years [1–8]. Blurred vision and oscillopsia typically occur early in the disease, often preceding the manifestations of the primary malignancy [1–8]. Malignancies most commonly associated with PCD include gynecologic, breast, small cell lung cancers, Hodgkin's lymphoma [1–8]. The combination of tumours and neurologic disability suggests the occurrence of effective anti-tumour autoimmunity, especially in cases with associated antibodies (anti-Yo and Ri, anti-Hu, anti-Tr and mGluR1) [1–8].

We read with interest the paper by Eye et al. [1], who described a patient with peculiar ophthalmological signs, anti-ZIC4 auto-antibodies, PCD associated with both diffuse large B cell lymphoma (DLBCL) and smoldering multiple myeloma. Eye's paper [1] expanded the knowledge on PCD, focusing on association between DLBCL and anti–ZIC4 auto-antibodies that preferentiallly target the Purkinje cells (Pcs). Having experienced a clinically similar case with unusually prolonged course, we wish to offer some comments.

A 53-year old woman was admitted because of acute onset of imbalance, impaired speech, inconstant diplopia on lateral gaze. On first admission (March 2002), neurological examination showed spontaneous downbeating nystagmus, diplopia with alternating skew deviation, head tremor, trunk and extremity ataxia, scanning dysarthria. Mentation, sensibility were normal and deep jerks brisk. Extensive examinations, including serum tocopherol, tumour markers, vitamin B_{12}, autoimmune and rheumathological tests, were unremarkable. Spinal fluid (CSF) showed 10 white cell/mm^3 with 80% lymphocytes which were CD3+ and CD4+, without detectable atypical cells. Reiber and Link indexes (1.62, normal < 0.70) were suggestive of intrathecal IgG synthesis. The patient had palpable thyroid, diagnosed as multinodular goiter. The increased titer of anti-thyroglobulin (495 UI/ml, NR 0-60) with normal thyroid function tests suggested an autoimmune thyroiditis. Antibodies to Hu, Ma2, Yo, Ri, calcium channel, CV2, amphiphysin were searched as previously reported [2,5] and found to be negative. Genetic analyses for inherited ataxias were unremarkable. In April 2002, nuclear and cytoplasmatic reactivity against Pcs in rat cerebellum frozen sections was detected. Western blotting, performed as previously described, [2,5] evidenced three bands of 39, 64 and 70 kDA not specifically identified, stronger in CSF (dilution 1:10) than in serum (1:500). These findings prompted concern for a remote tumour. The patient was screened with brain magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (FDG-PET), total body computed tomography (CT-scan), mammography, gastroscopy, colonoscopy, which were negative. Brain MRI repeated 10 months after onset showed cerebellar atrophy involving the vermis and cerebellar hemispheres with widening of infratentorial subarachnoid spaces and IV ventricle enlargement, which were out of proportion to the rest of the brain (Fig.1A, B). Bilateral symmetrical FLAIR hyperintensities, unenhanced after gadolinium, were seen in the dorso-mesial aspect of cerebellar hemispheres. These features were not compatible with active inflammatory process but consistent with reactive gliosis [7,8].In the same areas, a single voxel 144-TE MRI spectroscopy (MRS) showed decreased NAA/Cr and Cho/Cr ratio; such MRS metabolite pattern suggested a diminished neural integrity and low cell membrane turnover. During the following two years, the patient was tentatively treated with intravenous high doses of methylprednisolone and immunoglobulins monthly for 8 months without any benefit. Three further lumbar taps did not show any abnormality, except for the presence of oligoclonal bands. Two years after onset, suspecting a thyroid cancer, the patient underwent total thyroidectomy and histological examination revealed a marginal-zone B-cell lymphoma (Fig. 1C). The patient received oral chemotherapy with chlorambucil, obtaining complete metabolic remission. In the following 6 years, the patient exhibited worsened volitional tremor, severe trunk and limb ataxia, requiring wheelchair, but her mental state remained intact. In 2010, a total-body CT-scan revealed multiple subpleural and pulmonary nodules associated with cervical, supraclavicular, axillary lymphoadenopathies with increased FDG-uptake on PET, suggestive of transformation to high-grade lymphoma. Axillary lymphnode examination (Fig.1D) documented an activated B-cell type DLBCL. The patient received 6 cycles of chemoimmunotherapy, according to R-CHOP regimen [9]; her neurological conditions continued to deteriorate. In 2015, chest CT–scan detected a lung nodular lesion and supra and subdiaphragmatic lesions with high FDG-uptake were found at restaging PET-CT-scan. Atypical resection of left upper pulmonary lobe was performed on thoracotomy, with documentation of DLBCL relapse (Fig. 1E). The patient underwent a second-line chemoimmunotherapeutic program, based on 4 cycles of DHAOx-R regimen (dexamethasone, cytarabine, oxalyplatin, rituximab), followed by 9 cycles of lenalidomide [9]. Due to disease progression, further palliative

https://doi.org/10.1016/j.jns.2018.11.009
Received 9 August 2018; Received in revised form 10 October 2018; Accepted 6 November 2018
Available online 08 November 2018
0022-510X/

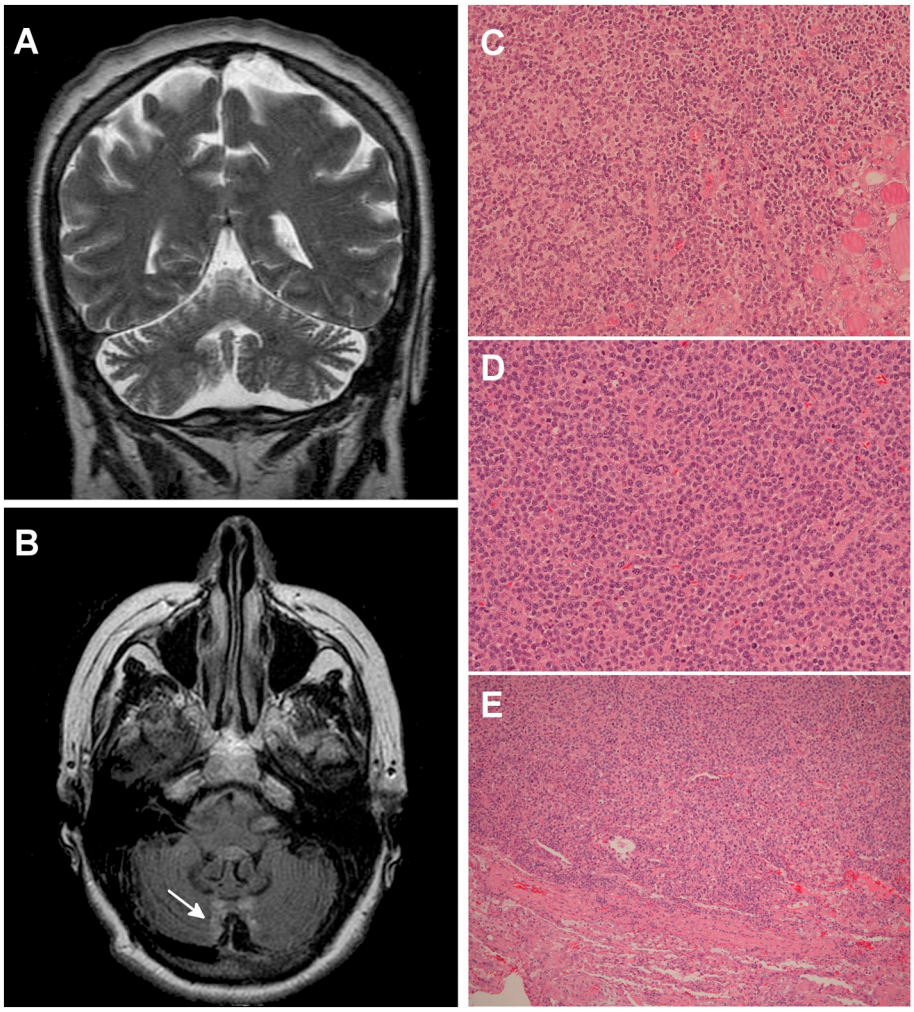

Fig. 1. Brain imaging and pathological results.
Coronal T2w (A) and transverse FLAIR (B) images, 10 months after onset revealed diffuse cerebellar atrophy associated with widening of infratentorial subarachnoid spaces. Bilateral symmetrical FLAIR hyperintensities (arrow) are seen in dorso-mesial aspect of cerebellar hemispheres; these hyperintensities did not show any enhancement after contrast and remained unchanged over time. In the same areas, MRS showed a decreased NAA/Cr and Cho/Cr ratio, suggestive of a diminished neural integrity and low cell membrane turnover. Brain stem and supratentorial structures were as expected from the patient's age.
(C) Marginal-zone B-cell lymphoma involving the right lobe and isthmus of thyroid. The tumour is composed of centrocyte-like cells, admixed with small lymphocytes and occasional plasma cells. Residual follicles can be seen in the lower corner. Nested polymerase chain reaction of the variable region of the immunoglobulin heavy chain gene showed a monoclonal FR3 band (HE, ×100, original magnification).
(D) Diffuse large B-cell lymphoma effacing the normal architecture of the lymphnode. The immunophenotype was CD20+, CD10-, bcl6+, bcl2+, MUM1+. Cytoproliferative activity (Mib-1) was 50% (HE, ×125, original magnification).
(E) Diffuse large B-cell lymphoma of the lung. Alveoli can be seen in the lower part of the picture (HE, ×100, original magnification).

chemotherapy with cyclophosphamide, doxorubicin and prednisone was administered. Death occurred in January 2017 due to respiratory failure.

Our case exhibited an abrupt onset mimicking a posterior vascular deficit. The subsequent clinical course had step evolution, at 2 years when a marginal-zone B-cell lymphoma was documented, at 8 years when a DLBCL was diagnosed and 13 years after onset, when DLBCL was discovered in the lung. It is interesting to note that the invasion of regional lymphnodes by tumour cells in PCD might be a prerequisite for triggering the pathological autoimmune process [2,5,7,10].

PCD usually deteriorate rapidly over weeks to months, but cases with prolonged course have been reported [1,6]. In our patient, a special comment deserves the imaging which was negative in early phases, showing over time a striking evolution toward a severe cerebellar atrophy. Such progression hints at a prolonged immunological process, possibly started long before symptom's appearance [7,8].Current diagnostic criteria define PCD as a pancerebellar syndrome of subacute onset with no evidence of atrophy on MRI other than that expected by the patient's age [6,7].

We could not identify in our case any known anti-onconeural antibodies, despite the fact that a paraneoplastic panel was repeated for anti-ZIC4, Hu, Ma2, Yo, Ri, calcium channel, CV2, VGKC, amphiphysin, obviously while the patient was receiving treatments. To the best of our knowledge, only 5 cases of PCD in non-Hodgkin lymphoma with associated auto-antibodies have been reported [1,5,11], including the one described by Eye et al. [1]. Briani et al. [5] described 5 patients with a PCD developed some months before tumour diagnosis: 2 had anti-Tr and 1 anti-Gad antibodies. Nonami et al. [11] 14 months after onset of PCD diagnosed a DLBCL of the stomach with detectable anti-Tr and mGluR1 auto-antibodies. In our patient, 6 months after onset of cerebellar signs, the observed cytoplasmatic and nuclear reactivity against PCs suggested an immune response specifically targeting the cerebellum [2,10]. In conclusion, our case deserves some practical lessons for clinicians: PCD can evolve insidiously with persistent chronic symptoms, MRI might mirror better than CSF an inflammatory reaction present in the nervous system [6,10], the association with DLBCL should be kept in mind, expanding the spectrum of PCD associated with hematological disorders [1,5,10–13].

Conflict of interest

None.

Disclosure

None of the authors have any financial or professional disclosures.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Aknowledgements

Professor Tullio Artusi originally evaluated a lymphnode biopsy.

References

[1] P.G. Eye, B. Wang, E.S. Keung, N.T. Tagg, Anti-ZIC4 associated paraneoplastic

cerebellar degeneration in a patient with both diffuse large B-cell lymphoma and incidental smoldering multiple myeloma, J. Neurol. Sci. 384 (2018) 36–37, https://doi.org/10.1016/j. jns. 2017.11.005.
[2] F. Graus, Recommended diagnostic criteria for paraneoplastic neurological syndromes, J. Neurol. Neurosurg. Psychiatry 75 (2004) 1135–1140, https://doi.org/10.1136/jnnp.2003.034447.
[3] N. Khan, Paraneoplastic cerebellar degeneration in a patient with anaplastic non-Hodgkin's lymphoma, BMJ Case Rep. 2018 (2018), https://doi.org/10.1136/bcr-2017-224100.
[4] D.G. Rodis, G.D. Liatsos, A. Moulakakis, M. Pirounaki, A. Tasidou, Paraneoplastic cerebellar degeneration: initial presentation in a patient with anaplastic T-cell lymphoma, associated with ichthyosiform cutaneous lesions, Leuk. Lymphoma 50 (2009) 1369–1371, https://doi.org/10.1080/10428190903030858.
[5] C. Briani, R. Vitaliani, W. Grisold, J. Honnorat, F. Graus, J.C. Antoine, G. Bertolini, B. Giometto, P.N.S. Euronetwork, Spectrum of paraneoplastic disease associated with lymphoma, Neurology 76 (2011) 705–710, https://doi.org/10.1212/WNL.0b013e31820d62eb.
[6] R. Scheid, R. Voltz, S. Briest, R. Kluge, D.Y. von Cramon, Clinical insights into paraneoplastic cerebellar degeneration, J. Neurol. Neurosurg. Psychiatry 77 (2006) 529–530, https://doi.org/10.1136/jnnp. 2005. 082206.
[7] J.H. Rees, Paraneoplastic cerebellar degeneration: new insights into imaging and immunology, J. Neurol. Neurosurg. Psychiatry 77 (2006) 427, https://doi.org/10.1136/jnnp. 2005. 082339.
[8] C. de Andrés, A. Esquivel, J.G. de Villoria, F. Graus, S. Sánchez-Ramón, Unusual magnetic resonance imaging and cerebrospinal fluid findings in paraneoplastic cerebellar degeneration: a sequential study, J. Neurol. Neurosurg. Psychiatry 77 (2006) 562–563 (doi:10. 1136/jnnp. 2005. 073379).
[9] H. Tilly, M. Gomes Da Silva, U. Vitolo, A. Jack, M. Meignan, A. Lopez-Guillermo, J. Walewski, M. André, P.W. Johnson, M. Pfreundschuh, M. Ladetto, ESMO guidelines committee, diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 26 (Suppl. 5) (2015), https://doi.org/10.1093/annonc/mdv304 v116–125.
[10] P. Schwenkenbecher, L. Chacko, R. Pul, K.-W. Sühs, F. Wegner, U. Wurster, M. Stangel, T. Skripuletz, Paraneoplastic cerebellar syndromes associated with antibodies against Purkinje cells, Int. J. Neurosci. 128 (2018) 721–728 (doi:10.1080/00207454. 2017. 1412967).
[11] A.Z. Nomani, M. Wazir, S.B. Kashmir, M.S. Qureshi, Diffuse large B-cell lymphoma of stomach presenting with paraneoplastic cerebellar degeneration syndrome, J. Coll. Physicians Surg. Pak. 24 (Suppl. 1) (2014) S11–S13 (doi: 03.2014/JCPSP.S11S13).
[12] Y. Shimazu, E.N. Minakawa, M. Nishikori, M. Ihara, Y. Hashi, H. Matsuyama, M. Hishizawa, S. Yoshida, T. Kitano, T. Kondo, T. Ishikawa, R. Takahashi, A. Takaori-Kondo, A case of follicular lymphoma associated with paraneoplastic cerebellar degeneration, Intern. Med. 51 (2012) 1387–1392, https://doi.org/10.2169/internalmedicine.51.7019.
[13] L.C. Ang, D.W. Zochodne, G.C. Ebers, J.C. Kaufmann, H.V. Vinters, Severe cerebellar degeneration in a patient with T-cell lymphoma, Acta Neuropathol. 69 (1986) 171–175 (3485877).

Giuliana Galassi[a,*], Maurilio Genovese[b], Fabio Forghieri[c], Alessandra Ariatti[a], Marcella Malagoli[b], Alessandra Melegari[d], Antonio Maiorana[e]
[a] *Department of Biomedical, Metabolic, Neural Sciences, University Hospitals of Modena, Italy*
[b] *Neuroradiology Unit, University Hospitals of Modena, Italy*
[c] *Section of Hematology, Department of Medical and Surgical Sciences, University Hospitals of Modena, Italy*
[d] *Department Integrated of Laboratory Medicine, Nuovo Ospedale Civile San Agostino Estense, Modena, Italy*
[e] *Institute of General Pathology, University Hospitals of Modena, Italy*
E-mail address: giulianagalassi@alice.it (G. Galassi).

[*] Corresponding author at: Department of Biomedical, Metabolic, Neural Sciences, University Hospitals of Modena, Via P. Giardini, 1355 Modena, Italy.