Journal of the Neurological Sciences 398 (2019) 117–118

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Letter to the Editor

A rapidly progressive motor neuron disease associated to a natural killer cells leukaemia

ARTICLE INFO

Keywords:
Motor neuron disease
Paraneoplastic
Leukaemia
NK-T cells.

Dear Sir,

Current hypotheses suggest that neuroinflammation and the immune system play a complex role, either protective or toxic, in ALS pathogenesis [1–3]. In particular, compelling evidence indicate that increased blood level of natural killer (NK) and NK-T cells may contribute to the disease development and progression [2,3].

Here, we report on a patient with an aggressive Motor Neuron Disease (MND) associated with NK/NK-T cells leukaemia.

1. Case report

A 79-year-old man presented with several months-history of a progressive atrophy and weakness of the upper limbs, which quickly spread to the lower limbs. Onset was subtle and apparently occurred in the month of July (the specific date is not shown for privacy), when the patient noticed a mild weakness in the proximal muscles of the right arm. From July through August, the patient's global functioning was however roughly normal. However, between September and early October the patient experienced a rapid worsening, with a severe weakness of the shoulder girdle, of the right arm and in both legs. He was referred to our ALS Center for evaluation. The neurological examination documented marked muscle atrophy of the shoulder girdle, the right arm and both lower limbs, with bilateral foot drop. Deep tendon reflexes were absent, with the exception of the left arm. Bulbar functions were normal. Needle EMG showed widespread polyphasic MUP and fibrillation potentials, with normal sensory and motor conduction velocities and no conduction blocks. Sensory and motor nerves amplitudes in the upper limbs were within the normal range. A brain and cervical MRI was within normal range. Extensive biochemical and immunological work-up, including CSF, blood cell count, a large antibody battery which included antibodies to anti-Hu, anti-Ri, anti-Yo, and anti-gangliosides were negative. Serum creatine phosphokinase level was mildly increased. A diagnosis of a very rapidly progressing lower motor neuron disease (MND) was made, with an ALSFRS-R score of 18/48 and a ΔFS [4] of 10 (Fig. 1A).

Although the clinical features of the patient did not fit with a formal diagnosis of ALS, a genetic testing for the major ALS related genes (*C9orf72*, FUS, TARDBP, SOD1, and Angiogenin) was performed, which gave negative results. In the middle of November 2016, a follow-up blood test showed a marked increase of WBC (i.e., 76,050/μL), with a high prevalence of lymphocytes.

He was then admitted to the Hematology Unit in our Hospital. Blood cytofluorimetric analysis and a bone marrow biopsy showed a marked infiltration by immature NK and NK-T cells (Fig. 1B). A new CSF analysis was performed, which showed increased proteins and 360/μL WBC, of which about 70% were NK/NK-T cells. A diagnosis of NK/NK-T cell leukaemia was made. A systemic chemotherapy according to Hyper-CVAD schema was started (i.e., High Dose Dexamethasone; Hyperfractionated Cyclophosphamide; Oncovine and Doxorubicine), along with repeated intrathecal injections with Methotrexate, Ara-C and Dexamethasone.

In the following weeks, the patient showed a transient improvement in muscle strength and function; a ALSFRS-R evaluation, made in December 2016, gave a score of 27/48, with a ΔFS dropping to 4.2 (Fig. 1A). Unfortunately, the general health status deteriorated over time, and in late December, the patient was referred to a Hospice, where a few weeks later he peacefully passed away.

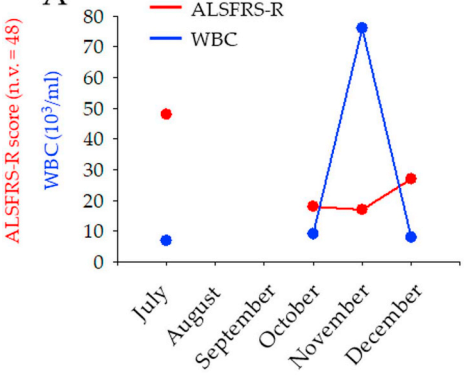
2. Discussion

We have described an aggressive lower MND, which might be paraneoplastic, associated with an NK-T leukaemia. A paraneoplastic association between either lower MND and lymphoma or the upper predominant MND and breast cancer has been reported [5–7].

The presence of a high number of NK/NK-T cells in the CSF indicates a meningeal metastasis from the acute leukaemia. These cells are most probably involved in the lower motor neuron degeneration in our patient. The clinical diagnosis of MND in this case is supported by several lines of evidence: a) the onset of atrophy and weakness occurred in the shoulder girdle, involving first the right shoulder with a rapid progression to the left shoulder, and then with a proximal-to-distal spreading to the right arm and then to the lower limbs. This pattern of spreading is consistent with a primarily MND involvement, rather than a poly/multi-neuropathy; b) the EMG/ENG pattern was also consistent with a lower motor neuron disease, as neither abnormal sensory/motor amplitudes (recorded in the in the upper limbs) nor conduction velocities/blocks (recorded in both the upper and lower limbs) could be detected. It cannot however be excluded a contemporary involvement of the motor neurons cell bodies and proximal section of the axons (i.e. the motor roots).

https://doi.org/10.1016/j.jns.2019.01.029
Received 17 December 2018; Received in revised form 7 January 2019; Accepted 15 January 2019
Available online 17 January 2019
0022-510X/ © 2019 Elsevier B.V. All rights reserved.

A



B

bone marrow cytofluorimetric analysis	
CD45	100%
CD3+	80%
CD7+CD3+	70%
CD8+CD3+	8%
CD4+CD3+	8%
CD2+CD3+	77%
CD16+CD56+CD3+	60%
CD16+CD56+CD3(-)	13%
CD57+CD3+	Neg
CD57+CD3(-)	Neg
TCR-ab+CD3+	77%
TCR-gd-CD3+	Neg

Fig. 1. A. Temporal profile of the ALSFRS-R total score (red circles) and white blood cells (WBC) counts (blue circles) in the patient. The ALSFRS-R score at onset was retrospectively evaluated as normal (score = 48). Note that the strong reduction of the ALSFRS-R score, indicating a rapid disease progression, was immediately preceding the sharp increase of the WBC counts.
B. Cytofluorimetric analysis of the bone marrow biopsy. Near 100% of cells were lymphocytes (CD45), with a high presence of T-cells (CD3, CD4, CD8) and a relevant pathologic presence of NK (CD16, CD56) and NK-T (CD16, CD56, CD3) cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Recent works have shown that NK/NK-T-cells are upregulated in ALS patients, suggesting an immune system activation. [2,3] In particular, in a longitudinal cohort study on the relationship between peripheral immunity and ALS, it was observed that NK cells increased in the patients' blood over time, and this has led to the suggestion that NK cells can negatively affect the disease progression, as they may indirectly drive the immune system towards a destructive response [3]. This hypothesis is supported by the evidence that NK-T cells were increased in the ALS SOD1G93A mouse, and that the pharmacological modulation of these cells with the α-GalCer analog PBS57 significantly extended survival [8]. Thus, a downregulation of the NK/NK-T might be beneficial in ALS.

The evidence that an aggressive MND might be related to an NK-T cell leukaemia, as in our patient, is a strong support to the hypothesis of a modulatory effect of NK/NK-T cells in ALS. With regard to our case, we speculate that the tumor cells, rather than directly causing the MND, might have played a role in unveiling the disorder and in driving its rapid evolution [3,8]. What variables are mainly involved in the disease onset of sporadic ALS is in fact at present unknown. After chemotherapy, ALSFRS-R score partially improved, but this might have been a non-specific effect on the patient's general health status. Its muscular atrophy did not change, and, besides the transient positive effect of the drugs administered, the leukaemia worsened leading the patient to a terminal stage.

In conclusion, this report adds to literature on the putative role of NK/NK-T cells in the pathophysiology of motor neuron degeneration. A better knowledge of the role of immune system in ALS might pave the way towards the discovery of new therapeutic approaches that might be beneficial in this neurodegenerative disorder.

Contributors

VLB: clinical case diagnosis, interpretation of the results, writing the final version of the manuscript. EI: clinical case diagnosis, interpretation of the results, writing the first version of the manuscript; LC: interpretation of the results, writing the first version of the manuscript; RS: clinical case diagnosis, interpretation of the results, writing the final version of the manuscript. VLB, EI, LC, RS: revising the manuscript.

Competing interests

None declared.

References

[1] K.G. Hooten, D.R. Beers, W. Zhao, S.H. Appel, Protective and toxic neuroinflammation in amyotrophic lateral sclerosis, Neurotherapeutics 12 (2015) 364–375.
[2] M. Rentzos, E. Evangelopoulos, E. Sereti, et al., Alteration of T cell subsets in ALS: a systemic immune activation? Acta Neurol. Scand. 125 (2012) 260–264.
[3] B.J. Murdock, T. Zhou, S.R. Kashlan, et al., Correlation of peripheral immunity with rapid amyotrophic lateral sclerosis progression, JAMA Neurol. 74 (2017) 1446–1454.
[4] F. Kimura, C. Fujimura, S. Ishida, et al., Progression rate of ALSFRS-R at the time of diagnosis predicts survival time in ALS, Neurology 66 (2006) 265–267.
[5] D.S. Younger, L.P. Rowland, N. Latov, et al., Lymphoma, motor neuron diseases, and amyotrophic lateral sclerosis, Ann. Neurol. 29 (1991) 78–86.
[6] P.A. Forsyth, J. Dalmau, F. Graus, et al., Motor neuron syndromes in cancer patients, Ann. Neurol. 41 (1997) 722–730.
[7] R. Spataro, V. La Bella, Paraneoplastic motor neuron disease associated with breast cancer, Eur. J. Neurol. 21 (2014) e5–e6.
[8] A. Finkelstein, G. Kunis, A. Seksenyan, et al., Abnormal changes in NKT cells, the IGF-1 axis, and liver pathology in an animal model of ALS, PLoS ONE 6 (2011) e22374.

Vincenzo La Bella[a,*], Emilio Iannitto[b], Luca Cuffaro[a], Rossella Spataro[c]
[a] *ALS Clinical Research Center, BioNeC, University of Palermo, 90129 Palermo, Italy*
[b] *Hematology Unit, Department of Oncology, University Hospital "P Giaccone", 90127 Palermo, Italy*
[c] *IRCCS Centro Neurolesi Bonino Pulejo, Palermo, Italy*
E-mail address: vincenzo.labella@unipa.it (V. La Bella).

* Corresponding author at: ALS Clinical Research Center, BioNeC, University of Palermo, Via G La Loggia, 1, 90129 Palermo, Italy.