Paraneoplastic cerebellar ataxia associated with anti-Hu antibodies and benign ganglioneuroma

We describe a case of cerebellar ataxia associated with anti-Hu antibodies and benign ganglioneuroma. A 28-year-old woman developed progressive ataxia with hyporeflexia at the age of 19. Brain MRI showed progressive cerebellar atrophy. Neurophysiological studies, screening of immune-mediated ataxias, oncological markers, vitamin E and genetic tests for spinocerebellar ataxia types 1, 2, 3, Friedreich ataxia and POLG1 were negative. Anti-Hu antibodies were positive in Western blot and indirect immunofluorescence (1:640). Total-body computed tomography revealed a mediastinum mass; the histological diagnosis was maturing ganglioneuroma. Immunohistochemistry showed a mild reaction between the tumor and the patient's serum, and no reaction between the tumor and control serum. After surgery, serum anti-Hu titer decreased, while ataxic symptoms initially worsened and then stabilized. Ganglioneuroma is a benign tumor, usually derived from the maturation of a neuroblastoma. The benign histology and the presence of anti-Hu antibodies could be related to the positive oncological prognosis and to the slow clinical course mimicking a degenerative ataxia.

KEY WORDS: anti-Hu antibodies, ganglioneuroma, immune-mediated ataxia, neuroblastoma, paraneoplastic syndrome.

Introduction

We describe the case of a woman presenting paraneoplastic cerebellar degeneration (PCD) associated with anti-Hu antibodies and ganglioneuroma, a neuroblastic tumor with a benign histology. PCD is a syndrome characterized by progressive cerebellar ataxia, related to the presence of a tumor, and possibly associated with onconeural antibodies (Graus and Dalmau, 2012). In pediatric patients, PCD may present with ocular and limb involuntary movements (opsoclonus-myoclonus-ataxia); in several affected children, the tumor responsible was found to be a neuroblastoma (Gambini et al., 2003).

Case report

The patient here described is a 28-year-old woman who developed progressive ataxia at the age of 19. She reported a history of scoliosis from the age of 4 years and fluctuating peripheral hearing impairment from the age of 10. At 14 years, brain MRI was normal, while at 23 years a control MRI study showed cerebellar atrophy without signal alterations. At the age of 25 years, neurological examination revealed moderate cerebellar gait, mild limb dysmetria, hyporeflexia in all four limbs, gaze-evoked horizontal nystagmus, and a mildly positive Romberg test; it was calculated that the patient would have scored 8/40 on the Scale for Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al., 2006). She never reported opsoclonus-myoclonus. Several diagnostic investigations gave normal findings, including complete neurophysiological studies, screening of immune-mediated ataxias, antibodies associated with celiac disease, oncological markers, alpha-fetoprotein,
vitamin E, acanthocytes, and genetic tests for spinocerebellar ataxia types 1, 2, 3, and Friedreich ataxia; molecular analysis of the \textit{POLG1} gene detected the known heterozygous mutation c803G>C (pG268A), while multiplex ligation-dependent probe amplification was negative. Anti-nuclear antibodies were found at variable titers, from negative to 1:640. Anti-Hu antibodies were positive in Western blot and indirect immunofluorescence performed on rat cerebellar slices (1:640). Two total-body positron-emission tomography scans showed mild non-specific tracer accumulations.

Total-body computed tomography (CT) scanning revealed, in the left superoposterior mediastinum, an expansive lesion with mild peripheral enhancement, and without compression or infiltration of adjacent structures or lymph node enlargement (Fig. 1, panels A and B). This mass was completely excised. Pathological examination, performed following the International Neuroblastoma Pathology Committee (INPC) recommendations (Shimada et al., 1999), described a 8x3x4 cm neuromatous proliferative mass, with a smooth surface, composed of spindle cells arranged in variably oriented bundles, distributed in a focally myxoid fibrovascular stroma; in this background, scattered neuron-specific-enolase-positive ganglion cells were observed, in some cases with prominent nucleoli or with two nuclei. Neuromatous cells expressed S100 protein. Neither defined nodules of neuroblasts nor necrosis, calcifications or inflammatory infiltrates were observed (Fig. 1, panel C). The histological diagnosis was ganglioneuroma, maturing subtype (Shimada et al., 1999).

To better characterize the possible relationship between anti-Hu antibodies and ganglioneuroma, we performed immunohistochemical assay by exposing tumor sections to the patient’s serum or to control serum; the tumor cells mildly reacted with the patient’s serum, while no immunoreaction was observed with the control serum (Fig. 1, panels D and E). After surgery, serum anti-Hu titers decreased (Table I), while gait ataxia and

Table I - Anti-Hu titers and therapeutic interventions during disease course.

<table>
<thead>
<tr>
<th>Time from tumor diagnosis (months)</th>
<th>Immunohistochemistry (serum anti-Hu titer)</th>
<th>Immunoblot positivity</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-surgery</td>
<td>Positive 1:640</td>
<td>3+</td>
<td>-</td>
</tr>
<tr>
<td>-1</td>
<td>-</td>
<td>-</td>
<td>Intravenous immunoglobulins</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
<td>Surgery</td>
</tr>
<tr>
<td>+4</td>
<td>Positive 1:160</td>
<td>2+</td>
<td>-</td>
</tr>
<tr>
<td>+6</td>
<td>Positive 1:320</td>
<td>1+</td>
<td>-</td>
</tr>
<tr>
<td>+8</td>
<td>Positive 1:80</td>
<td>&lt;1+</td>
<td>Intravenous immunoglobulins</td>
</tr>
<tr>
<td>+11</td>
<td>Positive 1:80</td>
<td>1+</td>
<td>-</td>
</tr>
<tr>
<td>+13</td>
<td>Positive 1:80</td>
<td>1+</td>
<td>-</td>
</tr>
<tr>
<td>+15</td>
<td>-</td>
<td>-</td>
<td>Intravenous steroids</td>
</tr>
<tr>
<td>+16</td>
<td>Positive 1:80</td>
<td>1+</td>
<td>-</td>
</tr>
<tr>
<td>+17</td>
<td>-</td>
<td>-</td>
<td>Plasma exchange</td>
</tr>
<tr>
<td>+18</td>
<td>Positive 1:40</td>
<td>1+</td>
<td>-</td>
</tr>
<tr>
<td>+20</td>
<td>-</td>
<td>-</td>
<td>Rituximab</td>
</tr>
<tr>
<td>+21</td>
<td>Positive 1:160</td>
<td>1+</td>
<td>-</td>
</tr>
<tr>
<td>+24</td>
<td>Positive 1:160</td>
<td>1+</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 1 - Radiological, pathological and immunohistochemical features of diagnosed ganglioneuroma.

A and B: Whole-body CT scan showing an expansive lesion in left superoposterior mediastinum (arrows). C: Hematoxylin-eosin staining of resected ganglioneuroma (original magnification x40). D and E: Patient’s ganglioneuroma sections exposed to patient’s serum (diluted 1:20, D) or control serum (diluted 1:20, E). (original magnification x20).
Paraneoplastic cerebellar ataxia and ganglioneuroma

disequilibrium first worsened and then stabilized; the
patient reached a SARA score of 13/40. Total-body CT,
cervical MRI, serum lactate dehydrogenase and urinary
vanil-mandelic and homovanillic acids were normal at
12 and 24 months after surgery, brain MRI was
unchanged at six and 24 months. Whole-body metaiodobenzyguanidine scintigraphy was negative.
The patient was treated with physical therapy, recurrent
oral steroids, two courses of intravenous immunoglobu-
lins, two courses of intravenous steroids, five courses
of plasma exchange, and two intravenous administra-
tions of rituximab (375 mg/m², separated by a two-week
interval), without significant effects (Table I).

Discussion

This case represents the first association of cerebellar
ataxia, anti-Hu antibodies and maturing ganglioneu-oma. Anti-Hu antibodies are defined as "well-character-
ed" onconeural antibodies, highly predicting the
presence of a tumor (Graus and Dalmau, 2012; Dal-
mau et al., 1995). They have already been described in
patients with opsoclonus-myoclonus-ataxia affected
by neuroblastoma (Dalmau et al., 1995; Salmaggi et
al., 1997; Jarius et al., 2009), but not in ataxic patients
with ganglioneuroblastoma or ganglioneuroma. More-
over, the Hu antigen is expressed in neuroblastoma
cell lines and in a proportion of neuroblastomas
(Dalmau et al., 1995).
The neuroblastic tumors lie along a histological con-
tinuum ranging from benign ganglioneuroma through
intermediate ganglioneuroblastoma to malignant neu-
roblastoma, with transitional subtypes (Shimada et
al., 1999). In our case, the presence of "well-character-
ed" antibodies (anti-Hu) and neurological syndrome
(PCD) allows the paraneoplastic syndrome to be diag-
nosed as "definite" in accordance with the diagnostic
criteria of Graus and Dalmau (2012). A possible patho-
genetic role of the ganglioneuroma is suggested by
the finding of an immunohistochemical reaction between
tumor antigens and the patient’s serum, and by the
reduction of the anti-Hu titer after tumor resec-
tion; the persistence of anti-Hu antibodies after surgi-
cal excision has already been described by others
(Jarius et al., 2009). We did not observe a significant
clinical improvement after surgical and pharmacologi-
cal treatment. In paraneoplastic syndromes, in fact,
the brain damage is due principally to cytotoxic T
cells, while anti-Hu antibodies, as well as other anti-
bodies against intracellular antigens, may be an
epiphenomenon; this may explain the persistence of
anti-Hu antibodies after surgical or pharmacological
therapy. Moreover, these data may be related to the
variable response to the treatments, as we observed
in our case.
Our patient, however, has some peculiarities, particu-
larly an older age at onset and a slower course of
ataxia compared with classical PCD associated with
neuroblastoma. It has been reported that neuroblas-
toma, usually proliferating and aggressive, may show
involution or spontaneous regression (Shimada et al.,
1999; Hero et al., 2008); a very uncommon evolution
of neuroblastoma is spontaneous and pathologically-
documented maturation into benign ganglioneuroma
even without treatment (Rothenberg et al., 2009;
Cushing and Wolbach, 1927; Fox et al., 1959; Haas et
al., 1988). Interestingly, the first report of spontaneous
maturation of neuroblastoma to gangli-neuroma is
also the first written description of opsoclonus-
myoclonus-ataxia syndrome associated with neurob-
lastoma (Cushing and Wolbach, 1927). Moreover, a
favorable prognosis has been described in some
malignant tumors (such as neuroblastoma and small
cell lung cancer) when associated with paraneoplastic
syndromes (Dalmau et al., 1995; Jarius et al., 2009;
Rothenberg et al., 2009; Altman and Baehner, 1976).
It could thus be hypothesized that our patient at an early
age developed a silent neuroblastoma which deter-
mined the synthesis of anti-Hu antibodies and matured
to ganglioneuroma; these two conditions could explain
the positive oncological prognosis and the slow clinical
course mimicking a degenerative cerebellar ataxia.

Acknowledgments

We wish to thank Drs Omar Racchi, Paola Tognetti,
Daria Schettini, and Giovanni Battista Ratto for their
expert contributions.

References

Altman AJ, Baehner RL (1976). Favorable prognosis for survival
in children with coincident opso-myoclonus and neuroblas-

Cushing H, Wolbach SB (1927). The transformation of a malig-
nant paravertebral sympathioblastoma into a benign gan-

patibility proteins, anti-Hu antibodies, and paraneoplastic
encephalomyelitis in neuroblastoma and small cell lung

Fox F, Davidson J, Thomas LB (1959). Maturation of sympa-
theticoblastoma into gangli-neuroblastoma: report of 2
patients with 20- and 46-year survivals respectively.

tumors associated with opsonolus-myoclonus syndrome:
histological, immunohistochemical and molecular features
of 15 Italian cases. Virchows Arch 442:555-562.

Graus F, Dalmau J (2012). Paraneoplastic neurological syn-

maturation and regression of stage IVS neuroblastoma

lastomas often show spontaneous regression: results of
the prospective trials NB95-S and NB97. J Clin Oncol
26:1504-1510.

anti-Hu associated adult neuroblastoma. J Neurol

association between neuroblastoma and opsonolus-