Title: Anti-Hu Antibody associated Paraneoplastic Cerebellar Degeneration in Head and Neck Cancer

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Author's response to reviews: see over
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Dear Professor Rades,

we submit herewith our revised manuscript entitled “Anti-Hu Antibody associated Paraneoplastic Cerebellar Degeneration in Head and Neck Cancer” for consideration as publication as a case report in BMC Cancer. We thank the reviewers for their helpful comments and further consideration of our manuscript. We addressed all issues raised in the manuscript (changes are highlighted in red) and in our point-by-point reply.

Following the evaluation of reviewer 1 this is a well presented case report with a comprehensive work-up. We totally agree that paraneoplastic cerebellar degeneration (PCD) has been reported in head and neck cancer in a few cases and also stated that in our manuscript. The association of PCD with anti-Hu antibody and spindle cell carcinoma, formerly called carcinosarcoma, has not been reported so far.

Reviewer 1

1. “Did the authors test the CSF for anti-Hu antibodies? It is well-known the better specificity of antibodies detection in the CSF for PCD. What about the results of CSF analyses in regards of cell count and chemistry?”
#1 Reply to the reviewer:

We thank the reviewer for these suggestions to improve our manuscript.

In our case, the cerebrospinal fluid was not tested for anti-Hu antibodies. According to the recommended diagnostic criteria for paraneoplastic neurological syndromes (Graus et al., Journal of Neurology, Neurosurgery & Psychiatry, 2004) the patient fulfilled the definition of a definite paraneoplastic neurological syndrome. Furthermore, Molinuevo et al. report a specificity of 99% and a sensitivity of 82% for an anti-Hu antibody for paraneoplastic syndromes in patients’ sera (Annals of Neurology, 1998). We totally agree that testing the cerebrospinal fluid for anti-Hu antibodies would have been of interest, but it was not required for establishing the diagnosis and would not have influenced our therapeutic decisions.

The analyses of two sequential lumbar punctures revealed a clear, colourless cerebrospinal fluid with cell counts and chemistry within normal limits in the absence of malignant cells. We stated the details in the revised manuscript. Serologic and PCR testing of both cerebrospinal fluid samples for viruses (Herpes simplex virus, Varicella zoster virus, Ebstein-Barr virus, Cytomegaly virus, Tick-borne encephalitis virus, Enterovirus), protozoa (Toxoplasma gondii) and bacteria (Listeria, Borrelia) were negative.

2. “What is the correlation of tumor staining for Hu antigen and PCD?”

#2 Reply to the reviewer:

Both, the primary tumor as well as the lymph node metastasis showed strong nuclear expression of the Hu-antigen without significant differences in staining intensity. However, a substantial fraction of cells in the lymph node metastasis appeared dedifferentiated (enlarged nuclei and cytoplasm) when compared with the primary tumor. The latter finding and altered antigen-presentation might explain the development of paraneoplastic cerebellar degeneration only upon disease relapse in this patient.
3. “Are the results of nerve conduction testing (especially the revealed the presence of demyelinating) consistent with the diagnosis?”

**#3 Reply to the reviewer:**

Nerve conduction studies revealed the presence of demyelinating and axonal polyneuropathy of the lower extremities. The presence of a mixed polyneuropathy is not a hallmark of paraneoplastic cerebellar degeneration. In a retrospective analysis by Camdessanché et al. (Brain, 2002), the association of anti-Hu antibodies with paraneoplastic peripheral neuropathy has been demonstrated in a series of 20 patients. In the absence of other factors that could have contributed to the patient’s abnormal nerve conduction studies, we conclude that the patient’s peripheral neuropathy may also have been caused by paraneoplastic mechanisms.

4. “Did the MRI of the brain revealed any signs of cerebellar degeneration?”

**#4 Reply to the reviewer:**

Several magnetic resonance imaging studies of the brain were carried out, neither of them showed any cerebellar abnormalities– we addressed the issue in more detail in the revised manuscript.

**Reviewer 2:**

1 “The CSF examination is reported as being "unremarkable". In the name of completeness the authors should state whether CSF cytology was performed to help rule out meningeal involvement the tumor, which in itself could have contributed to the clinical syndrome.”

**#1 Reply to the reviewer:**

After the onset of the neurological complaints in January 2010, a lumbar puncture was carried out on 01/30/2010 followed by a second spinal tap on 02/25/2010. The analyses of both procedures revealed a clear, colourless cerebrospinal fluid with cell
counts and chemistry within normal limits in the absence of malignant cells. We stated the details in the revised manuscript. Serologic and PCR testing of both cerebrospinal fluid samples for commonly tested viruses (Herpes simplex virus, Varicella zoster virus, Ebstein-Barr virus, Cytomegaly virus, Tick-borne encephalitis virus, Enterovirus), protozoa (Toxoplasma gondii) and bacteria (Listeria, Borrelia) was negative.

#2 “The sentence on lines 140-141 regarding Carboplatin does not make sense to me as written. The authors should revise this sentence to make it more clear to the reader.”

#2 Reply to the reviewer:

In the light of the patient’s documented neuropathy, carboplatin AUC (area under the curve) 5 was preferred over cisplatin for concomitant use with radiotherapy due to its lower neurotoxic potential and was intravenously applied on day 1 of each cycle. The sentence was revised as suggested.