Author's response to reviews

Title: Multicentric Castleman's disease with voltage-gated potassium channel antibody-positive limbic encephalitis: a case report

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Version: 2 Date: 18 December 2014

Author's response to reviews: see over
Dear Editor,

We appreciate the Reviewers’ insightful questions and thoughtful comments about our manuscript, “Multicentric Castleman’s disease with voltage-gated potassium channel antibody-positive limbic encephalitis: a case report.” We have revised the manuscript to address all of the Reviewers’ concerns. Please find below the original comments of each Reviewer in italics followed by our detailed responses in regular style. The revised manuscript with all changes highlighted will be uploaded as a separate file, and we hope it is now acceptable for publication in BMC Neurology.

Sincerely,

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REVIEWER 1

Minor Essential Revisions

1. The patient discussed developed deficits in memory and “intermittent disorientation,” leading (along with his documented seizures) to a diagnosis of limbic encephalitis. How were his memory deficits characterized? Were episodes of intermittent disorientation related to the spells described or were they separate? Did these cognitive symptoms improve following immunotherapy? If a formal neuropsychological evaluation was performed at symptom onset or later in the patient’s course, this could be referenced here.

The patient’s memory deficits were characterized by subjective report from the patient, by collateral history—his girlfriend noticed increased forgetfulness at home—and by bedside neurological exam (1/3 object recall after 5 minutes). The patient’s girlfriend also described episodic “confusion” coinciding with the patient’s spells, and a subset of the seizures captured during video-EEG monitoring involved clear dyscognitive semiology. We suspect that his episodic mental status changes were ictal/post-ictal phenomena, and that his progressive memory difficulty resulted from a high burden of temporal lobe seizures. The patient’s cognitive deficits improved after initiation of valproex, even prior to the start of immunotherapy, and formal neuropsychological testing was not pursued.

We have revised the text to clarify these points.
2. It is somewhat misleading to refer to anti-VGKC-complex antibody-mediated syndromes as “paraneoplastic” since, as the authors note, most cases are not associated with an underlying malignancy.

We agree that limbic encephalitis (LE) associated with VGKC antibodies is typically non-paraneoplastic. However, our patient meets criteria for a definite paraneoplastic neurological syndrome: a classical syndrome (e.g. LE) and cancer that develops within five years of the diagnosis of the neurological disorder [1]. The expert committee that formulated these criteria state that the presence of VGKC antibodies “should not be used to exclude a paraneoplastic cause of the limbic encephalitis” [1].

Several lines of evidence are supportive in this regard:

1. VGKC subtypes have been identified in tumor cells, including neuroendocrine tumors (e.g. small-cell lung carcinoma), retinoblastoma, oligodendroglioma, melanoma, leiomyosarcoma, and hematologic malignancies [2]. This suggests that VGKC’s are potentially relevant autoantigens initiating paraneoplastic autoimmunity.
2. In a series of patients with suspected autoimmune or paraneoplastic neurological disorders who were found to have VGKC antibodies, 34/80 (47%) had some evidence of underlying neoplasia [3].
3. In another series, VGKC antibodies were found in patients with both paraneoplastic (lung cancer) and idiopathic forms of LE [4].
4. VGKC antibody-positive LE has been reported in the setting of acute myeloid leukemia [5], indicating that malignant hemopathies can produce paraneoplastic syndromes with atypical antibody associations.

For these reasons, we have retained the term “paraneoplastic” in the manuscript.

Discretionary Revisions

1. The authors may wish to refer to the patient’s limbic encephalitis syndrome and other features characteristic of anti-VGKCc (such as hyponatremia) earlier in their report (e.g., in the abstract, rather than focusing only on his seizures there).

In the revised manuscript, we include the finding of hyponatremia in the abstract.

2. The authors may wish to note the characteristic faciobrachial dystonic seizures seen in a large minority of patients with anti-LGI-1 antibodies (Irani et al. 2013), and comment that this patient’s movements, uncharacteristically of these, do not involve dystonic posturing of the arm — if that is indeed the case.

We have revised the manuscript to clarify that our patient did not demonstrate the faciobrachial dystonic seizures that often precede onset of LE in LGI-1 antibody-positive patients, and we reference Dr. Irani’s original description of this association [6].

3. Did the patient also have CSF antibodies tested? Was a broader autoimmune work-up sent along with the antibody tests already discussed, and if so were any additional antibodies positive? (This is the case in 10%-20% of anti-VGKCc patients and may be indicative of a broader autoimmune response. It would
be interesting to see if this was more likely in this case in the setting of Castleman’s syndrome.) It may not be possible at this point to test specifically for the VGKC proteins LGI-1 and CASPR-2, but if possible this would be very helpful, both because the result would be more specific than the serum RIA and because the associated syndromes vary significantly in treatment-responsiveness and in the likelihood of an underlying neoplastic process.

The patient did not have CSF antibody testing. Due to resource limitations, only select antibodies were tested in serum (VGKC, NMDAR, GAD), and VGKC antibodies were not further characterized, but we agree that more specific testing might have yielded valuable diagnostic and prognostic information.

4. Was there any additional work-up for underlying neoplastic disease? (The authors describe only their lymph node biopsy — was this based on a PET/CT that was otherwise unremarkable?)

Initially, the patient had a body PET/CT that was non-diagnostic, showing diffuse radiotracer uptake in muscle suggestive of inappropriate fasting. A repeat study was interpretable and revealed diffuse, hypermetabolic lymphadenopathy (mild-moderate \(^{18}\text{F}-\text{FDG}\) avidity in innumerable lymph nodes) but no other evidence of neoplastic disease. At the time, the scan was read as suspicious for lymphoma, though, in retrospect, it is also consistent with Castleman’s disease. Results of this study have been added to the manuscript.

5. It would be useful to include a sense of how often Castleman’s is diagnosed in the setting of a negative HHV-8.

HHV-8 is present in all HIV-positive patients and approximately 50% of HIV-negative patients with multicentric Castleman’s disease [7, 8]. The manuscript has been revised to include this figure.

REVIEWER 2

1. During neurological workup, did you consider performing imaging modalities (CT, MRI or PET/CT) to amend the CSF and EEG results?

Yes. A 3.0 Tesla gadolinium-enhanced brain MRI was normal, and this result is described in the original manuscript. We also performed body PET/CT that showed diffuse hypermetabolic lymphadenopathy. Rostral images from this scan only included the base of the brain, which was normal. PET/CT results have now been added to the manuscript.

2. VEGF expression is considered to have an important role in angiogenesis of Castleman disease. In the pathology report, do you have information about that?

We did not check serum levels or perform immunohistochemical staining for VEGF because it was not necessary to secure the diagnosis. However, the result would have been interesting, and we appreciate the proposed role of VEGF in vascular proliferation in Castleman’s disease [9, 10].
3. VGKC antibody levels remained elevated after treatment showing the poor response of the patient. What other therapeutic options did you consider, other than siltuximab?

In addition to siltuximab (IL-6 antibody) [11], we considered tocilizumab (IL-6 receptor antibody) [12], bortezomib (proteasome inhibitor) [13], other chemotherapy regimens (R-CHOP, RCVP, thalidomide), and autologous stem cell transplantation [14].

4. Did you measure IL-6 levels in response to therapy?

We did not monitor IL-6 levels following initiation of rituximab. Instead, we followed the patient’s response to therapy clinically and with serial PET/CT scans.

The criteria for evaluating response to therapy in Castleman’s disease have not been firmly established [15], and biochemical measures could certainly play a role. Serum IL-6 levels correlate with clinical abnormalities in Castleman’s disease [16], but IL-6 dynamics during treatment of Castleman’s disease appear to be therapy-dependent. For example, treatment with rituximab leads to reduction in IL-6 levels [17] whereas treatment with tocilizumab, an antibody against the IL-6 receptor, causes serum IL-6 levels to rise [18]. Thus, we predict that IL-6 levels in our patient would decrease over time, but we did not test this directly.

REVIEWER 3

1. There is an enlarged lymph node on the first CT. What is the reason that you didn’t do a biopsy from it, and wait for 9 months for the next diagnostic step?

Following the chest CT, our patient underwent a considerable amount of diagnostic testing, including body PET/CT, multiple bronchoscopies with transbronchial lung biopsy, fine needle aspiration (FNA) of a cervical lymph node, and serological tests, all of which required several months to complete on an outpatient basis. Workup for seizures proceeded in parallel during this time. When FNA and bronchoscopic evaluations proved non-diagnostic, excisional lymph node biopsy was pursued and ultimately revealed the diagnosis.

2. Did perform PET alone or PET/CT? Were there any abnormalities on these in the brain?

We performed body PET/CT which revealed diffuse, hypermetabolic lymphadenopathy. The most rostral images from this scan only covered the base of the brain, which was normal. These results have now been added to the manuscript.

3. How often did you monitor IL-6 level? It would be helpful if you show the change of the cytokines and antibodies level correlate with the treatment in a graph.

We did not monitor IL-6 levels following initiation of rituximab. Instead, we followed the patient’s response to therapy clinically and with serial PET/CT scans.
The criteria for evaluating response to therapy in Castleman’s disease have not been firmly established [15], and biochemical measures could certainly play a role. Serum IL-6 levels correlate with clinical abnormalities in Castleman’s disease [16], but IL-6 dynamics during treatment of Castleman’s disease appear to be therapy-dependent. For example, treatment with rituximab leads to reduction in IL-6 levels [17] whereas treatment with tocilizumab, an antibody against the IL-6 receptor, causes serum IL-6 levels to rise [18]. Thus, we predict that IL-6 levels in our patient would decrease over time, but we did not test this directly.

4. VGKC antibody levels and IL-6 were elevated after the treatment. What other therapeutic options did you consider?

We have considered several other treatment options, including: siltuximab (IL-6 antibody) [11], tocilizumab (IL-6 receptor antibody) [12], bortezomib (proteasome inhibitor) [13], other chemotherapy regimens (R-CHOP, RCVP, thalidomide), and autologous stem cell transplantation [14].

REFERENCES


