| タイトル | Title | Cerebral angiitis associated with subarachnoid hemorrhage in Castleman’s disease: report of two cases |
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| 著者 | Author(s) | Tanaka, Jun / Fujita, Atsushi / Hosoda, Kohkichi / Kohmura, Eiji |
| 掲載誌・巻号・ページ | Citation | BMC Neurology, 16:60 |
| 刊行日 | Issue date | 2016-05-04 |
| 資源タイプ | Resource Type | Journal Article / 学術雑誌論文 |
| 版区分 | Resource Version | publisher |

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| DOI | 10.1186/s12883-016-0585-4 |
| JaLCDOI | |
| URL | http://www.lib.kobe-u.ac.jp/handle_kernel/90003434 |

PDF issue: 2018-11-04
Cerebral angiitis associated with subarachnoid hemorrhage in Castleman’s disease: report of two cases

Jun Tanaka*, Atsushi Fujita, Kohkichi Hosoda and Eiji Kohmura

Abstract

Background: Multicentric Castleman’s disease (MCD) is characterized by a systemic lymphoproliferative disorder affecting systemic lymph nodes. Cerebrovascular involvements have rarely been reported, and to our knowledge, cerebral angiitis causing subarachnoid hemorrhage (SAH) in patients with Multicentric Castleman’s disease (MCD) has not been previously described.

Case presentation: We identified two cases of MCD with SAH who were receiving immunosuppressive therapy with low dose prednisolone. Both patients presented with sudden-onset headache and were diagnosed with cortical SAH in the sulci by a computed tomography scan. Digital subtraction angiography showed segmental stenosis in the peripheral area of the middle cerebral artery. In both cases, cerebral angiitis causing SAH induced by a systemic inflammatory condition and elevated levels of interleukin (IL) -6 were suspected and resolved over a period of several months.

Conclusion: Our cases highlight the clinical diversity of the potential causes of cerebral angiitis and expand the association of MCD and cortical SAH; however, cortical SAH patients have a more favorable outcome than aneurysmal SAH patients.

Keywords: Castleman’s disease, Subarachnoid hemorrhage, Cerebral angiitis, Interleukin-6

Background

Castleman’s disease (CD) was initially described by Benjamin Castleman et al. in 1956 as a disease with solitary hyperplastic mediastinal lymph nodes containing small, hyalinized follicles and a marked interfollicular vascular proliferation [1]. CD is caused by infection of human herpesvirus 8 (HHV-8) and human immunodeficiency virus (HIV). Such viral infections cause B cells in the lymph nodes to excessively release interleukin (IL) -6 or similar polypeptides and cause several autoimmune clinical symptoms [2]. CD is classified into two subgroups, unicentric Castleman’s disease (UCD) and multicentric Castleman’s disease (MCD). UCD usually affects one lymph node area and the patients are often asymptomatic. In contrast, MCD affects systemic lymph nodes and the patients present various symptoms, such as hyperthermia, lymphadenopathy, splenomegaly, hepatomegaly, pulmonary disorders, edema, and ascites. MCD also may be associated with a variety of malignant diseases, such as Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, POEMS syndrome: polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinemia and skin changes [2]. About the vascular involvements of MCD, temporal arteritis [3] and some cases of coronary and lower limb vascular involvements have been described. In general, it is unusual that the patients of MCD will present neurological symptoms, and intracranial involvements of the MCD have been rarely reported in the literature to date [4]. An association of MCD with some types of intracranial tumors, such as chordoid meningioma and clear cell meningioma, has been reported in some cases [5]. The pathogenesis of MCD in cases with such intracranial tumors remains unclear, but a complex cytokine network, including IL-6, IL-1β and vascular endothelial growth factor (VEGF), may contribute to the growth of the tumor [6]. Although there are

* Correspondence: jun_flatout@yahoo.co.jp
Department of Neurosurgery, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

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some reports of cerebrovascular involvements in patients with MCD, all of the presented cases had ischemic stroke caused by cerebral angiitis secondary to a systemic inflammatory condition, as indicated by excessive serum levels of IL-6 [7, 8]. To our knowledge, no reports are currently available about cerebral angiitis causing subarachnoid hemorrhage (SAH) in patients with MCD. Here, we describe two rare cases of MCD associated with cerebral angiitis leading to SAH.

**Case presentation**

**Case 1**

A 57-year-old woman was admitted to a nearby hospital because of respiratory discomfort due to exercise, where a laboratory examination showed high levels of serum gamma globulin. She was then referred to our hospital for further examination. On admission, her physical examination showed a swelling of the lymph nodes of the mediastinum and axillary fossa. Laboratory examination showed anemia (hemoglobin: 3.9 g/dl), hypoalbuminemia (1.5 g/dl), hypergammaglobulinemia (IgG: 8140 mg/dl, normal: 870–1700 mg/dl, IgA: 851 mg/dl, normal: 110–410 mg/dl, IgM: 297 mg/dl, normal: 46–260 mg/dl) and an elevation of serum levels of C-reactive protein (CRP) (9.8 mg/dl). The serum IL-6 level was 43.5 pg/ml (normal < 4.0 pg/ml). An HIV viral examination was negative. HHV-8 examination was undone. A chest X-ray showed a reticular shadow of bilateral lung fields. Histopathological examination by transbronchial lung biopsy (TBLB) to lung lesions showed plasmacytic proliferation. The histopathological findings led to her to be diagnosed as MCD, and we started to administrate prednisolone orally (50 mg/day). Thrombocytopenia or coagulopathy (including anticoagulant-induced) was not identified based on the laboratory findings, and any other infection or autoimmune disorder was excluded. Three months after admission to our hospital, she suddenly felt a strong headache. She was alert and presented no apparent neurological deficit. The level of immunoglobulins and other laboratory findings were similar to those recorded previously. Her blood pressure was 148/88 mmHg, and her other vital signs were within normal range. A head computed tomography (CT) scan showed cortical SAH along the left frontal sulci (Fig. 1a). Further evaluation by fluid-attenuated inversion recovery
and VEGF in MCD, however they concluded the
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term administration of prednisolone was expected to
tion of the disease was relatively stable, but the long-
home and continued prednisolone therapy. The condi-
was introduced to our hospital because she moved to a
oral prednisolone (20 mg/day). At 58 years of age, she
was diagnosed with MCD at 57 years old and started
tion of plasmacyte around vessels within true skin. She
splenomegaly. Biopsy of the lesion showed the prolifera-
agulopathy. A chest and abdominal CT scan showed an
showed that she had neither thrombocytopenia nor co-
HHV-8 examination was undone. Past examinations
level (131 pg/ml). HIV viral examination was negative.
IgA: 798 mg/dl, IgM: 765 mg/dl) and an elevation of
(2.1 g/dl), hypergammaglobulinemia (IgG: 6627 mg/dl,
found anemia (hemoglobin: 9.1 g/dl), hypoalubuminemia
any other abnormal findings. A laboratory examination
tical examination did not find swelling of lymph nodes or
other abnormal findings. A laboratory examination
anemia and hypergammaglobulinemia at an annual
20 years ago. At 51 years of age, she was diagnosed with
A 59-year-old woman found a rash on her abdomen
Case 2
A 59-year-old woman found a rash on her abdomen
20 years ago. At 51 years of age, she was diagnosed with
anemia and hypergammaglobulinemia at an annual
health checkup. For further examination, she was admitted
to a general hospital near her home. There, a phys-
tical examination did not find swelling of lymph nodes or
any other abnormal findings. A laboratory examination
found anemia (hemoglobin: 9.1 g/dl), hypoalbuminemia
(2.1 g/dl), hypergammaglobulinemia (IgG: 6627 mg/dl,
IgA: 798 mg/dl, IgM: 765 mg/dl) and an elevation of
serum levels of CRP (9.8 mg/dl) and the serum IL-6
level (131 pg/ml). HIV viral examination was negative.
HHV-8 examination was undone. Past examinations
showed that she had neither thrombocytopenia nor co-
agulopathy. A chest and abdominal CT scan showed an
interstitial shadow at the bilateral lung fields and mild
splenomegaly. Biopsy of the lesion showed the prolifera-
tion of plasmacyte around vessels within true skin. She
was diagnosed with MCD at 57 years old and started
oral prednisolone (20 mg/day). At 58 years of age, she
was introduced to our hospital because she moved to a
home and continued prednisolone therapy. The condi-
tion of the disease was relatively stable, but the long-
term administration of prednisolone was expected to
risk systematic complications. We started to infuse
tocilizumab, a humanized anti-human IL-6 receptor
antibody, and decreased the dose of prednisolone to
12.5 mg/day. One day, she was admitted to the emerg-
ency room of our hospital complaining of sudden-on-
set headache, and she was alert and presented no appar-
etent neurological deficit. Her blood pressure was rela-
tively high (180/90 mmHg), and other laboratory
findings, including the level of immunoglobulin E, were
almost within normal ranges. Head CT showed subtle
cortical SAH along the right parietal sulci (Fig. 2a).
FLAIR images showed the distribution of cortical SAH
in right parietal sulci (Fig. 2b). The emergent right in-
ternal cerebral angiography, late arterial phase, showed
stenosis and post-stenotic delayed opacification in the
area of the peripheral middle cerebral artery; this perfu-
sion area corresponded to the location of SAH (Fig. 2c).
The follow-up DSA after one week after onset showed
the disappearance of both stenosis and disturbed perfu-
sion (Fig. 2d), and her headache got better and also the
focal deficit was not presented. After 1-year from the
discharge, cortical SAH was completely disappeared and
no other vascular lesion was detected by the follow-up
MRI, and no other event was recognized in the follow-
up period.

Discussion
Only in some cases in MCD, the cerebrovascular in-
volvments of ischemic stroke due to cerebral angiitis
have been reported, especially in the cases of MCD with
POEMS syndrome [7, 8]. Rössler M et al. reported on a
case of young female with POEMS syndrome presented
recurrent ischemic stroke due to cerebral vasculitis. In
this case, DSA showed the segmental stenosis of prox-
imal ACA [9]. Garcia T et al. described two cases of
POEMS syndrome and MCD accompanied with recur-
rent ischemic stroke, in which DSA showed diffuse non-
atherosclerotic segmental stenosis of the intracranial
arteries. They hypothesized that the stenosis might be in-
duced by the overproduction of cytokines, such as IL-6,
IL-1β and VEGF in MCD, however they concluded the
pathogenesis remained unclear [10]. Among these in-
flammatory biomarkers, IL-6 is well known to play an
important role in acute inflammatory response triggered
by cerebral ischemia, and an elevated blood IL-6 con-
centration is associated with poor outcome after stroke
[11]. Moreover, a higher level of serum IL-6 is also asso-
ciated with an increased risk of recurrent vascular events
after stroke [9]. Despite these conclusive findings in both
acute and chronic phases that clearly indicate an important
role of IL-6 in stroke patients, these associations are
not fully understood. According to these reports, elevated
levels of IL-6 might be a major causal factor in the
occurrence of cerebral angiitis in our patients with MCD
and a lasting chronic over-expression of IL-6. Further
research is required to substantiate the role of these biomarkers and to determine whether any of them may serve as a prognostic factor or therapeutic target to prevent cerebral angiitis in MCD.

On the other hand, there is no report of hemorrhagic stroke due to cerebral angiitis in patients with MCD. In our two cases of MCD accompanied with SAH, it is pathognomonic that both cases presented with cortical SAH isolated along sulci, and both cases are accompanied with the segmental stenosis of peripheral intracranial arteries. The stenosis in these cases may be due to angiitis and SAH induced by the vulnerability of the arterial wall. This hypothesis is supported by the fact that the angiographic findings of angiitis appeared not only in intracranial arteries but also in bilateral renal arteries in case 1. As previously reported, the prognosis of patients with cortical SAH carried a favorable outcome than that of aneurysmal SAH [12]. Despite the presence of severe vasoconstriction, ischemic stroke, and cortical SAH, our case also experienced a favorable outcome, so a noninvasive imaging work-up, such as CT angiography or MR angiogram, should be introduced after an initial DSA does not identify any other underlying etiology.

Because there is no conclusive test that can be used to diagnosis cerebral angiitis, it is crucial to exclude the many other conditions that can mimic the symptoms of cerebral angiitis. First, patients with clinical and imaging features, such as severe headache, variable neurological deficits, and reversible arterial abnormalities (dilatations and stenosis), can be separately recognized as the reversible cerebral vasoconstriction syndrome (RCVS). Approximately one-third of patients with RCVS develop ischemic stroke, lobar hemorrhage, or convexal SAH. RCVS-related SAH likely results from dynamic caliber changes affecting cortical surface vessels, and it is also usually restricted to 1 to 2 sulcal spaces [13]. In our cases, reversible imaging findings were compatible with RCVS; however, we believe that the systemic inflammatory condition (i.e., MCD) possibly explained the reversible vasoconstriction. Second, the stenosis of intracranial arteries may be the ultra-early vasospasm that occurred immediately after SAH. Qurehi AI et al. reported in their study that 13 % of patients had evidence of ultra-early vasospasm (within the first 48 h), and the vasospasms were mild (vessel narrowing of 25–50 %) in 78 % of these patients [14]. Although immediate vasospasm of cortical SAH has been suspected, coexistence with these has never been reported in the literature. A possible explanation of this was that a small amount of extravascular blood of the cortical SAH has less local effect on cerebral arteries compared to aneurysmal one.

Fig. 2 Neuroimaging findings of Case 2. a CT scan of the head shows a subtle cortical subarachnoid hemorrhage along the right parietal sulci (arrow heads). b FLAIR sequence of the MRI shows the distribution of a subarachnoid hemorrhage (arrow heads). c Lateral magnified view of the right internal carotid angiogram, late arterial phase, shows a stenosis (arrow) and post-stenotic delayed opacification in the area of peripheral middle cerebral artery. d Lateral magnified view of the right internal carotid angiogram obtained one week after onset shows a disappearance of stenotic findings and normal perfusion (arrow)
Third, the long-term administration of glucocorticoid may also introduce the atherosclerotic stenosis of intracranial arteries. In such a case, the stenosis should not be segmental but widespread to all intracranial arteries, and we believe that it is difficult for the stenosis to recovery angiographically in such a short period. Moreover, the symptoms present relative slowly, not drastically. At present, we require additional careful considerations that distinguish RCVS or other possible causes from these systemic conditions until further studies can be performed.

Conclusions
We identified two cases of MCD who presented with sudden-onset headache and were diagnosed with cortical SAH. In both cases, cerebral angiitis causing SAH induced by a systemic inflammatory condition due to MCD. Our cases highlight the clinical diversity of the potential causes of cerebral angiitis and expand the association of MCD and cortical SAH.

Ethics and consent to participate
The authors declare that ethics approval was not required for this case report.

Consent for publication
In case 1, written informed consent for publication of this case report and any accompanying images was obtained from the patient’s family because she had passed away. In case 2, written informed consent was also obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials
The dataset supporting the conclusions of this article is included within the article.

Abbreviations
ACA: anterior cerebral artery; CD: Castleman’s disease; CRP: C-reactive protein; CT: computed tomography; DSA: digital subtraction angiography; FLAIR: fluid-attenuated inversion recovery; HHV-8: human herpesvirus 8; HIV: human immunodeficiency virus; IL-6: interleukin-6; MCA: middle cerebral artery; MCD: multicentric Castleman’s disease; POEMS: polynuropathy, organomegaly, endocrinopathy, monoclonal proteinemia and skin changes; RCVS: reversible cerebral vasocnstriction syndrome; SAH: subarachnoid hemorrhage; TBLB: transbronchial lung biopsy; UCD: unicentric Castleman’s disease; VEGF: vascular endothelial growth factor.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
EK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors. Drafting of the manuscript: JT. Critical revision of the manuscript for important intellectual content: All of the authors. Study supervision: AF, EK. All authors have read and approve of the final version of the manuscript.

Acknowledgements
The authors are grateful for useful advice and suggestions from Dr. Hiroki Kawano, Dr. Yasuhiro Funada, and Dr. Yoshio Katayama. They also thank their patients and his families for participating in this study.

Funding
The authors declare that they obtained no funding for this study.

Received: 25 September 2015 Accepted: 30 April 2016
Published online: 04 May 2016

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