Tumor-Like Presentation of Primary Angiitis of the Central Nervous System

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Background and Purpose—We aimed to describe the clinical and imaging features of patients with tumor-like presentation of primary angiitis of the central nervous system.

Methods—We retrospectively analyzed 10 patients enrolled in the French primary angiitis of the central nervous system cohort, who initially presented tumor-like brain lesions and compared them with other patients within the cohort.

Results—The 10 patients with tumor-like presentation were younger and had more seizures at diagnosis than the other 75 patients (median of 37 [30–48] years versus 46 [18–79] years; P=0.008; 9 [90%] with seizures versus 22 [29%], P<0.001; respectively). All 10 patients had a biopsy (stereotactic procedure in 7 and open-wedge surgery in 3). Histological findings suggestive of vasculitis were observed in 9 patients in whom conventional cerebral angiography and magnetic resonance angiography were negative. In the remaining patient, vascular imaging demonstrated diffuse bilateral large- and medium-sized vessel involvement (biopsy did not reveal vasculitis). All patients with tumor-like presentation received glucocorticoids, combined with cyclophosphamide in 9 cases. With a median follow-up of 27 (12–130) months, 5 (50%) patients relapsed, but achieved remission again after treatment intensification.

Conclusions—Patients with tumor-like presentation of primary angiitis of the central nervous system represent a subgroup characterized with mainly small-sized vessel disease that requires histological confirmation because vascular imaging is often normal. Although relapses are not uncommon, global outcomes are good under treatment with glucocorticoids and cyclophosphamide. (Stroke. 2016;47:2401-2404. DOI: 10.1161/STROKEAHA.116.013917.)

Key Words: biopsy ■ mass ■ primary angiitis of the central nervous system ■ tumor ■ tumor-like presentation

Primary angiitis of the central nervous system (PACNS) is a rare inflammatory disease involving CNS vessels. Diagnosis is challenging because presentation is highly polymorph, and an extensive work-up is required to exclude mimicking conditions and identify potential causes, such as infections or neoplasms.1–3 Few cohort series improved our knowledge of PACNS and suggested the existence of subgroups with different presentation and outcomes.1,2,4,5 The aim of the present study was to describe the clinical and imaging features of the 10 patients with a tumor-like presentation of PACNS enrolled in the French multicentre cohort.

Methods

Patients

We initiated a cohort of patients with definite diagnosis of PACNS (COVAC [Cohort of Patients With Primary Vasculitis of the Central Nervous System]) in 2010 in France using the well-established networks of the French Vasculitis Study Group, French NeuroVascular Society, and National Society of Internal Medicine. This cohort has been supported by an institutional grant from the French Ministry of Health (COVAC, 2009 PHRC 08017). In brief, all patients were aged >18 years, had a follow-up of >6 months from diagnosis (unless they had died before), and had a complete work-up to exclude systemic vasculitis, connective tissue disease, infection, malignancy, and any other diseases possibly involving CNS. They all exhibited CNS vessel...
involvement on brain biopsy (n=26), digital subtraction angiography (n=49), and magnetic resonance angiography (n=10). We excluded patients with a presentation compatible with vasculopathy (unless they had a positive biopsy), such as atherosclerosis or reversible cerebral vasoconstriction syndrome. The cohort now includes 85 patients (a report on the first 52 patients was published in 2014). For the present study, we specifically looked at those patients with tumor-like presentation of PACNS at diagnosis. They all had (1) an isolated neurological disorder and (2) brain magnetic resonance imaging (MRI) work-up at diagnosis, demonstrating unique or multiple contrast-enhanced mass(es) or infiltrative lesion(s), with perilesional edema and mass effect, not linked to ischemic lesions on diffusion-weighted imaging, and (3) demonstration of vascular involvement on biopsy or digital subtraction angiography.

**Studied Variables and Definitions**

Using a standardized form, characteristics of each patient were retrieved from their medical records, as described earlier. Neuroimaging studies were centrally reviewed by 2 neuroradiologists (G. Boulouis and O. Naggara) unaware of clinical manifestations. Results of MRI were collected. As performed previously, we differentiated large-, medium-, and small-sized vessels. Intracranial internal carotid and proximal anterior (A1), middle (M1), and posterior (P1) cerebral arteries were considered large; second divisions (A2, M2, and P2) and subsequent branches (>A2, >M2, and >P2) were considered medium- and small-sized, respectively. When available, magnetic resonance spectroscopy results were collected, as well as those of repeated MRI at the end of treatment.

**Statistical Analyses**

Categorical variables are expressed as number (%) and quantitative variables as median (range). Categorical variables were analyzed with the Chi-square or Fisher exact test, as appropriate, and quantitative variables with Wilcoxon’s rank-sum test. Statistical analyses were computed with GraphPad Prism (5.0c). A P value ≤0.05 defined statistical significance.

**Results**

Characteristics of the 10 patients with tumor-like presentation identified in the cohort are shown in Table (Table I in the online-only Data Supplement). All had a biopsy (stereotactic procedure in 7 and open-wedge surgery in 3), and histological findings suggestive of vasculitis were observed in 9, including 8 (89%) with a lymphocytic pattern. The patient with a negative biopsy (histological samples contained little brain tissue) had diffuse bilateral large- and medium-sized vessel involvement on magnetic resonance angiography and digital subtraction angiography and exhaustive negative investigations that ruled out other conditions. In 4 patients, immunohistochemistry studies on biopsy samples combined with gene rearrangement studies excluded lymphoproliferative disease.

Seven patients showed masses on MRI (single and multiple lesions in 4 and 3 cases, respectively), with edema and mass effect in 3 and 5 cases, respectively (Figure). In 3 other patients, MRI showed white matter infiltrative lesions with edema and mass effect. Three patients underwent magnetic resonance spectroscopy, the results of which were not suggestive of malignant process.

When compared with patients from the cohort without tumor-like presentation, the 10 patients were younger (median, 37 [30–48] years versus 46 [18–79] years; P=0.008) and more presented with seizures at diagnosis (9/10 (90%) versus 22/75 (29%); P≤0.001). Except for the patient with a noncontributory biopsy, the other 9 patients had negative digital subtraction angiography and magnetic resonance angiography, suggestive of isolated small-sized vessel PACNS.

Nine of the 10 patients with tumor-like presentation received glucocorticoid combined with cyclophosphamide (6 pulses, given over a median of 5 [3–6] months). With a
median follow-up of 27 (12–130) months, 5 (50%) patients had a relapse. Repeated MRI (performed 4–8 months after cyclophosphamide initiation) revealed persistent lesions in all patients, with a stable appearance in 2 cases and improvement in 8. Gadolinium enhancement gradually disappeared in all.

**Discussion**

Tumor-like presentation is a rare feature of PACNS and has not been thoroughly characterized8,9 (Table II in the online-only Data Supplement). According to the previous literature, the present series shows that most patients with tumor-like PACNS have a negative vascular imaging, which suggests a preponderant small-vessel involvement. In this setting, biopsy remains crucial for diagnosis. Immunostainings and combined gene rearrangement studies, as performed in 4 patients of the present series, are useful for differentiating PACNS from lymphoma. In the study from Molloy et al, a granulomatous pattern was observed on histological study in 53% of the cases and lymphocytic pattern in the others.9 In the present series, however, the lymphocytic vasculitis pattern was the rule.

Although the 10 patients were younger than others from our PACNS cohort and had more seizure and gadolinium enhancements, we did not identify clinical or radiological signs specific enough to suggest a PACNS in a patient with tumor-like presentation. Outcomes were favorable in our patients using the combination of glucocorticoids and cyclophosphamide, although relapses were not uncommon. In relapsing or refractory patients, rituximab could probably represent an alternative option.10

The retrospective design and the small sample size are 2 limitations of our study and may have precluded the identification of small differences between patient subgroups. Nevertheless, because the 10 patients were extracted from one of the largest cohort PACNS ever reported, we assume that our findings offer new insights on the peculiar subgroup of patients with PACNS and tumor-like presentation. In addition, patient population was self-selected or referred to 25 tertiary centers, raising the possibility of referral bias and artificially increasing incidence of tumor-like PACNS. Finally, functional imaging, such as magnetic resonance spectroscopy, was not routinely performed in our cohort, precluding the identification of differences before biopsy between malignant neoplasm and tumor-like PACNS.

In conclusion, our study highlights the characteristics of patients with tumor-like presentation of PACNS. Although these patients showed nonspecific clinico-radiological differences from those without such tumor-like lesions, diagnostic and therapeutic approaches are similar. Biopsy is mandatory to demonstrate vasculitis and rule out other conditions, especially malignancy. Treatment, although not validated by prospective trials, should include a combination of glucocorticoids and immunosuppressant.

**Sources of Funding**

This study was supported by an institutional grant from the French Ministry of Health (COVAC, 2009 PHRC 08017).

**Disclosures**

None.
References


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http://stroke.ahajournals.org/content/47/9/2401

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Supplemental Methods

Review of the literature and selection.

The medical literature on the tumoral presentation of PACNS was reviewed from January 1990 to February 2016, inclusively, using PubMed (including MEDLINE and Pre-MEDLINE databases), limiting searches to adults. We used the following keywords: “primary angiitis of the central nervous system” or “primary cerebral vasculitis” or “primary central nervous system vasculitis”, which were each linked to “tumor-like”, “mass”, “tumor”, “tumoral” or “pseudotumoral”. All relevant articles were retrieved and any additional references quoted in these articles were checked.

We only retained articles reporting patients with 1) definite diagnosis of PACNS obtained with diagnosis criteria according to Mallek and Calabrese; 2) tumoral presentation defined as single or multiple space-occupying parenchymal lesion(s); 3) available MRI described in the publication; 4) peer-reviewed publication; 5) individual patient data and 6) in English or French.

In some studies, only subsets of patients met the inclusion criteria and only these were included.

We used a data-extraction form subdivided into 4 sections: 1) baseline characteristics, 2) biological and histological exploration, 3) imaging data and 4) outcomes.

Supplemental Results

Data from the literature

We identified 37 articles, mostly single case reports or short series of a few patients and excluded 18 of them because of lack of individual detailed information, including the study with literature review from Molloy et al. References given within these articles were checked and included in our analysis if individual data was available.

Detailed data was available in the 19 selected articles for a total of 22 patients (male/female: 11/11; median age 42 [20-80] years), whose main characteristics are described in Supplemental Table II.

Focal deficit was the most frequent presenting symptom in 12 (54%) patients, followed by headaches in 11 (50%). Imaging revealed a single mass in 13 (62%) patients, supratentorial in 11 and involving the spinal cord in two. In seven other patients, MRI demonstrated multiple supratentorial well-delimited masses including infratentorial and spinal cord involvement in one. In two other patients, MRI showed white matter infiltrative lesions.

Vascular imaging results were available for 18 patients and were normal in 14 (78%). All 22 patients presented histological evidence of vasculitis with lymphocytic pattern being the most frequent. This was observed in 17 (77%) patients.
Twenty patients were treated with GC, and 14 received GC combined with CYC. Six patients also had a surgical resection of their lesions, which was the only treatment in two cases. Follow-up information was available for 16 patients. Two had relapsed and were being treated with higher dose of GC and CYC. The two patients who underwent resection only did not relapse. Two patients died and six patients had persistent disabilities.
**SUPPLEMENTAL TABLES**

**Supplemental Table I.** Characteristics of the 10 patients with tumour-like presentation of PACNS

<table>
<thead>
<tr>
<th>Patient, age</th>
<th>Clinical manifestations</th>
<th>Tumour localisation</th>
<th>Type of biopsy</th>
<th>Histology result</th>
<th>CCA result</th>
<th>MRA result</th>
<th>Treatment</th>
<th>Relapse</th>
<th>Follow-up (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, 34</td>
<td>Headaches, seizures, impaired vigilance</td>
<td>Left frontotemporal lobe</td>
<td>Stereotactic</td>
<td>Ly</td>
<td>Normal</td>
<td>Normal</td>
<td>GC + CYC, AZA</td>
<td>Yes</td>
<td>22</td>
</tr>
<tr>
<td>Male, 30</td>
<td>Headaches, focal deficit, aphasia, seizures, cognitive disorder</td>
<td>Right temporal lobe</td>
<td>Stereotactic</td>
<td>Nec</td>
<td>Normal</td>
<td>Normal</td>
<td>GC + CYC</td>
<td>Yes</td>
<td>59</td>
</tr>
<tr>
<td>Male, 48</td>
<td>Headaches, focal deficit, aphasia, seizures, impaired vigilance</td>
<td>Right frontotemporal lobe</td>
<td>Open-wedge</td>
<td>Ly, Nec, gra</td>
<td>Normal</td>
<td>Normal</td>
<td>GC + CYC, AZA</td>
<td>Yes</td>
<td>51</td>
</tr>
<tr>
<td>Male, 31</td>
<td>Headaches, focal deficit, seizures</td>
<td>Left parietal lobe</td>
<td>Open-wedge</td>
<td>Negative</td>
<td>Diffuse bilateral large- and medium-sized vessel involvement</td>
<td>GC + CYC</td>
<td>No</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Female, 37</td>
<td>Headaches, focal deficit, seizures, cognitive disorder, impaired vigilance</td>
<td>Left occipital lobe</td>
<td>Stereotactic</td>
<td>Ly, nec</td>
<td>ND</td>
<td>Normal</td>
<td>GC + CYC, AZA</td>
<td>No</td>
<td>13</td>
</tr>
<tr>
<td>Male, 42</td>
<td>Aphasia, seizures, cognitive disorder</td>
<td>Left temporal lobe</td>
<td>Stereotactic</td>
<td>Ly, nec</td>
<td>Normal</td>
<td>Normal</td>
<td>GC + CYC, AZA</td>
<td>No</td>
<td>14</td>
</tr>
<tr>
<td>Male, 33</td>
<td>Aphasia, seizures, cognitive disorder, impaired vigilance</td>
<td>Left hemisphere</td>
<td>Open-Wedge</td>
<td>Ly</td>
<td>Normal</td>
<td>Normal</td>
<td>GC + CYC</td>
<td>No</td>
<td>26</td>
</tr>
<tr>
<td>Female, 37</td>
<td>Seizures</td>
<td>Right frontal lobe</td>
<td>Stereotactic</td>
<td>Ly</td>
<td>ND</td>
<td>Normal</td>
<td>GC</td>
<td>No</td>
<td>12</td>
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<tr>
<td>Age</td>
<td>Gender</td>
<td>Symptoms</td>
<td>Lobe</td>
<td>Procedure</td>
<td>Finding</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>Other</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>39</td>
<td>Female</td>
<td>Headaches, focal deficit, aphasia</td>
<td>Right parieto-occipital lobe</td>
<td>Stereotactic</td>
<td>Ly</td>
<td>Normal</td>
<td>ND</td>
<td>GC + CYC</td>
<td>Yes, 50 mo.</td>
</tr>
<tr>
<td>42</td>
<td>Female</td>
<td>Headaches, focal deficit, seizures, cognitive disorder</td>
<td>Left temporo-parietal lobe</td>
<td>Stereotactic</td>
<td>Ly, nec</td>
<td>Normal</td>
<td>ND</td>
<td>GC + CYC, AZA</td>
<td>Yes, 5 mo.</td>
</tr>
</tbody>
</table>

Ly: lymphocytic; Nec: necrosis; gra: granulomatous; ND: not done; GC: glucocorticoids; CYC: cyclophosphamide; AZA: azathioprine; mo.: month
**Supplemental Table II. Literature review of patients with tumoral presentation of PACNS**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gender, age</th>
<th>Clinical symptoms</th>
<th>Tumoral localisation</th>
<th>Vascular imaging</th>
<th>CSF</th>
<th>Biopsy</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan C. et al. 2015,7</td>
<td>M, 51</td>
<td>Headaches, aphasia, cognitive disorder,</td>
<td>Unique supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Positive</td>
<td>GC + CYC</td>
<td>-</td>
</tr>
<tr>
<td>Killeen T, et al., 2015</td>
<td>M, 51</td>
<td>Headaches</td>
<td>Unique supratentorial</td>
<td>Normal Abnormal</td>
<td>Abnormal</td>
<td>Lymphocytic</td>
<td>Res + GC</td>
<td>Independent</td>
</tr>
<tr>
<td>Lyra TG, et al., 2013</td>
<td>M, 28</td>
<td>Focal deficit, aphasia,</td>
<td>Multiple supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Lymphocytic</td>
<td>GC + CYC</td>
<td>Relapse, Independent</td>
</tr>
<tr>
<td>Tanei T. et al., 2011</td>
<td>M, 60</td>
<td>Dysarthria</td>
<td>Multiple supratentorial</td>
<td>Normal Normal</td>
<td>Lymphocytic</td>
<td>Res</td>
<td>Disabled</td>
<td></td>
</tr>
<tr>
<td>You G. et al., 2011</td>
<td>F, 35</td>
<td>Headaches, focal deficit</td>
<td>Unique supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Lymphocytic</td>
<td>Res + GC + CYC</td>
<td>Independent</td>
</tr>
<tr>
<td>Kinsella JA et al., 2010</td>
<td>F, 80</td>
<td>Focal deficit, cognitive disorder</td>
<td>Unique supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Necrosis</td>
<td>GC + CYC</td>
<td>Independent</td>
</tr>
<tr>
<td>Kumar RS et al., 2010</td>
<td>F, 44</td>
<td>Headaches, focal deficit, aphasia, dysarthria</td>
<td>Multiple supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Lymphocytic</td>
<td>GC + CYC</td>
<td>Disabled</td>
</tr>
<tr>
<td>Lee Y et al., 2009,13</td>
<td>F, 37</td>
<td>Dysarthria, cognitive disorder</td>
<td>Unique supratentorial</td>
<td>Stenoses</td>
<td>-</td>
<td>Lymphocytic</td>
<td>GC + CYC</td>
<td>-</td>
</tr>
<tr>
<td>Lee Y et al., 2009,13</td>
<td>M, 24</td>
<td>Seizures</td>
<td>Unique supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Lymphocytic</td>
<td>Res + GC</td>
<td>-</td>
</tr>
<tr>
<td>Lee Y et al., 2009,13</td>
<td>M, 23</td>
<td>Focal deficit</td>
<td>Multiple supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Lymphocytic</td>
<td>GC + CYC</td>
<td>-</td>
</tr>
<tr>
<td>Name et al., Year</td>
<td>Gender Age</td>
<td>Symptoms</td>
<td>Location</td>
<td>Morphology</td>
<td>Pathological Findings</td>
<td>Treatment</td>
<td>Outcome</td>
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<tr>
<td>Lee Y et al., 2009</td>
<td>F, 29</td>
<td>Focal deficit</td>
<td>Multiple supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Lymphocytic GC</td>
<td>-</td>
<td></td>
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<tr>
<td>Qu S-B, et al., 2009</td>
<td>F, 50</td>
<td>Headaches, focal deficit, cognitive disorder</td>
<td>Unique supratentorial</td>
<td>Stenoses Abnormal</td>
<td></td>
<td>Lymphocytic GC + CYC, MTX</td>
<td>Disabled</td>
<td></td>
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<tr>
<td>Yin Z et al., 2009</td>
<td>F, 25</td>
<td>Headaches, focal deficit</td>
<td>Unique supratentorial</td>
<td>Distal stenoses Normal</td>
<td></td>
<td>Lymphocytic and necrosis GC</td>
<td>Independent</td>
<td></td>
</tr>
<tr>
<td>Nabika S, et al. 2008</td>
<td>F, 68</td>
<td>Dysarthria, cognitive disorder</td>
<td>Multiple supratentorial, infratentorial and spinal cord</td>
<td>- Normal</td>
<td></td>
<td>Lymphocytic and granulomatous GC</td>
<td>Died</td>
<td></td>
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<tr>
<td>Baumer D et al. 2008</td>
<td>M, 64</td>
<td>Focal deficit</td>
<td>Unique spinal cord</td>
<td>- Abnormal</td>
<td>Positive</td>
<td>GC + CYC</td>
<td>Disabled</td>
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<tr>
<td>Beppu T, et al. 2007</td>
<td>M, 30</td>
<td>Headaches, cognitive disorder, seizures</td>
<td>Unique supratentorial</td>
<td>Distal stenoses Normal</td>
<td></td>
<td>Granulomatous and necrosis Res + GC</td>
<td>Relapse, Disabled</td>
<td></td>
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<tr>
<td>Panchal NJ, et al., 2005</td>
<td>F, 25</td>
<td>Headaches, focal deficit</td>
<td>Multiple supratentorial</td>
<td>-</td>
<td></td>
<td>Lymphocytic GC + CYC</td>
<td>Disabled</td>
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<tr>
<td>Hashizume Y, et al., 2004</td>
<td>M, 65</td>
<td>Headaches</td>
<td>Unique supratentorial</td>
<td>Abnormal</td>
<td></td>
<td>Lymphocytic GC + CYC</td>
<td>Died</td>
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<td>Calabrese LH, et al., 2003</td>
<td>M, 40</td>
<td>Headaches, seizures</td>
<td>Unique supratentorial</td>
<td>Normal Normal</td>
<td></td>
<td>Lymphocytic GC + CYC</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Krummert B, et al., 2010</td>
<td>M, 44</td>
<td>Headaches, focal deficit, seizures</td>
<td>Multiple supratentorial</td>
<td>Normal</td>
<td>-</td>
<td>Lymphocytic GC + CYC</td>
<td>Independent</td>
<td></td>
</tr>
</tbody>
</table>
PACNS: primary angiitis of the central nervous system; CSF: cerebrospinal fluid; GC: glucocorticoids; CYC: cyclophosphamide; Res: resection; RT: radiotherapy; MTX: methotrexate
Supplemental References


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