Atypical Reversible Leucoencephalopathy Syndrome after Bevacizumab/Folfox Regimen for Metastatic Colon Cancer

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1. Introduction
Leucoencephalopathy postchemotherapy is a very rare complication that affects the central nervous system. Posterior reversible leucoencephalopathy syndrome (PRLS) is the most described in the literature [1]; it is characterized by an impairment of the white matter of the posterior cerebral hemispheres. In some cases, this syndrome can affect the anterior hemispheres, gray matter, brainstem, and basal ganglia [2–4].

We describe an unusual case of diffuse leucoencephalopathy syndrome after chemotherapy based on Folfox-Bevacizumab (5 FU: 325 mg/m² d1 by intravenous infusion, Oxaliplatin 80 mg/m² d1, and Bevacizumab: 7.5 mg/Kg d1) affecting the central nervous system.

2. Case Presentation
We are presenting a case of a 44-year-old female, without any particular medical history. She is treated for a metastatic colon cancer for which she received chemotherapy based on Folfox-Avastin (5 FU: 325 mg/m² d1 by intravenous infusion, Oxaliplatin 80 mg/m² d1, and Bevacizumab: 7.5 mg/Kg d1).

She has received a total of four cures. The blood pressure and the proteinuria were controlled at each cure and they were normal. The first three cures were well tolerated except a grade II diarrhea. During the fourth cure, the patient has developed laryngeal spasm during the infusion of Oxaliplatin; a day after chemotherapy, she has presented with a deviation and hypoesthesia of the tongue associated with swallowing disorders; the blood pressure was 17/9 mmhg.

Due to this clinical figure, we performed a computed tomography (CT) of the brain which showed hypodense lesions of the white matter of frontal, parietal, and occipital lobes, which were bilateral and symmetrical. The clinical table was reversible under symptomatic treatment.

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Given this clinical figure, another brain computed tomography was performed in the fifth day resulting in hypodense, symmetrical, and bilateral lesions of the white matter of the frontal, parietal, and occipital area (Figure 1). The patient was treated with intravenous nicardipine, 1 mg every 15 minutes until normalization of the blood pressure and oral phenobarbital 150 mg a bid. After 48 hours of monitoring, we found that the blood pressure was back to normal (12/7 cmHg); then the antihypertensive therapy was not necessary. We did not give her a steroid therapy and we maintain oral phenobarbital.

Few days under symptomatic treatment, neurological examination showed a gradual return to normal and complete resolution of the neurological deficit. The diagnosis of postchemotherapy leucoencephalopathy was retained. The chemotherapy was stopped and the patient died two months later due to the progression of her disease.

3. Discussion
Posterior reversible leucoencephalopathy syndrome was first introduced in 1965 by Hinchey et al. [1]. In fact, it is probably a misnomer; this syndrome is not always reversible and is not necessarily limited to the posterior regions of the brain.

The pathophysiology of this syndrome remains debatable; it involves a diffusion of plasmatic proteins into the extracellular space. Two hypotheses have been advanced: the vasogenic and cytotoxic theories.

In the first hypothesis, the increase in blood pressure exceeding the cerebral autoregulation leads to a vasodilatation and a formation of vasogenic edema [1, 5, 6].

In the second hypothesis, it suggests that a brutal and significant increase in blood pressure produces a cerebral vasoconstriction with an ischemia which causes an injury of endothelial cell and the formation of cytotoxic edema [5, 7].

Headache is the most sign found in the clinical figures [5, 7–10]; seizures have been reported in most series [1, 5, 8, 10, 11]; they are often resolutive after management of PRLS and after discontinuation of the responsible agent. However in some pediatric series the evolution has been done to the status of epilepsy disease [12, 13]. Altered mental status as lethargy, confusion, and disorientation in time and space has also been reported frequently in the literature [8, 9].
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient (age, sex)</th>
<th>Localization</th>
<th>Chemotherapy</th>
<th>Symptoms</th>
<th>MRI</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sawaya et al., 2014 [18]</td>
<td>31 W</td>
<td>Ovarian carcinoma</td>
<td>Bevacizumab</td>
<td>Focal tonic-clonic seizure BP: not mentioned</td>
<td>Cortical and subcortical lesions of the parietal, occipital, and frontal lobes, posterior fossa, left pons, left cerebral peduncle</td>
<td>Intravenous benzodiazepines, phenytoin, and valproic acid</td>
<td>The patient recovered slowly over a fortnight</td>
</tr>
<tr>
<td>Dersch et al., 2013 [19]</td>
<td>41 W</td>
<td>Lung cancer</td>
<td>Gemcitabine-cisplatin Bevacizumab</td>
<td>Grand mal seizures, nausea, vomiting, limb ataxia, visual hallucinations, confusion, headache BP: 180/110 mmHg at admittance with peaks to 245/140 mmHg</td>
<td>Bifrontal, parietal, temporal, thalamic, and cerebellar lamina T2-hyperintensive lesions</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lazarus et al., 2012 [20]</td>
<td>72 M</td>
<td>Lung cancer</td>
<td>Maintenance Bevacizumab (patient received paclitaxel-carboplatin and Bevacizumab before)</td>
<td>Emesis, aphasia, altered mental status, agitation, myoclonus, tonic-clonic seizures, BP: 164/75</td>
<td>Bilateral cortical hyperintensities, involving the occipital lobes and cerebellar hemispheres</td>
<td>Enoxaparin</td>
<td>Worsening of lesions patient died</td>
</tr>
<tr>
<td>Lau and Paunipagar, 2011 [21]</td>
<td>63 W</td>
<td>Metastatic rectosigmoid carcinoma</td>
<td>Intravenous Bevacizumab in combination with oxaliplatin and 5-fluorouracil</td>
<td>Headache, drowsiness, visual disturbance, no focal neurological signs in the limbs vital signs were stable (BP: not mentioned)</td>
<td>Complete spontaneous clinical recovery within 1 week</td>
<td>Supportive measures</td>
<td>Signal abnormalities in the subcortical white matter in the posteroinferior parietotemporal lobes</td>
</tr>
<tr>
<td>Seet and Rabinstein, 2012 [17]</td>
<td>68 W</td>
<td>Metastatic non-small cell lung carcinoma</td>
<td>Intravenous Bevacizumab in combination with taxol and carboplatin</td>
<td>Headaches, confusion, nausea, and vomiting BP 221/84 mmHg</td>
<td>Cerebellar lesions on MRI brain</td>
<td>Intravenous labetol</td>
<td>Neurologic recovery one day later MRI changes resolved 8 days later</td>
</tr>
<tr>
<td>Seet and Rabinstein, 2012 [17]</td>
<td>63 W</td>
<td>Advanced pancreatic carcinoma</td>
<td>Intravenous Bevacizumab in combination with gemcitabine and oxaliplatin</td>
<td>Seizures and cortical blindness BP 190/94 mmHg</td>
<td>Parietooccipital lesions on MRI brain</td>
<td>Oral antihypertensive medications</td>
<td>Neurologic recovery 4 days later MRI changes resolved 30 days later</td>
</tr>
<tr>
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<tr>
<td>Levy et al., 2009 [22]</td>
<td>4 M</td>
<td>Hepatoblastoma</td>
<td>Intravenous Bevacizumab in combination with gemcitabine and oxaliplatin</td>
<td>Seizures, headache, BP: 160/120 mmHg</td>
<td>Frontal and parieto-occipital subcortical lesions on MRI brain</td>
<td>Antihypertensive medications (details not mentioned)</td>
<td>Neurologic deficits resolved 13 days later MRI changes resolved 21 days later</td>
</tr>
<tr>
<td>Bürki et al., 2008 [23]</td>
<td>33 W</td>
<td>Metastatic breast cancer</td>
<td>Intravenous Bevacizumab in combination with liposomal doxorubicin</td>
<td>Headaches, gastalgia, nausea, and vomiting, BP: 150/100 mmHg.</td>
<td>Frontal and parieto-occipital subcortical lesions on MRI brain</td>
<td>Intravenous infusion of prednisolone, furosemide, nicardipine, and mannitol</td>
<td>Neurologic recovery 1 day later MRI changes resolved 4 days later</td>
</tr>
<tr>
<td>El Maalouf et al., 2008 [24]</td>
<td>55-year-old woman</td>
<td>Metastatic colon cancer</td>
<td>Intravenous Bevacizumab in combination with fluorouracil and leucovorin</td>
<td>Lethargy, dysarthria, and generalized seizures BP 180/120 mmHg</td>
<td>Pontomedullary lesions on MRI brain</td>
<td>Oral amlodipine</td>
<td>Neurologic deficits resolved 1 day later MRI changes resolved 21 days later</td>
</tr>
<tr>
<td>Koopman et al., 2008 [25]</td>
<td>49 M</td>
<td>Colorectal cancer</td>
<td>Intravenous Bevacizumab in combination with oxaliplatin and capecitabine</td>
<td>Unconsciousness, seizures, and urinary incontinence BP 180/100 mmHg</td>
<td>Occipital lesions on CT brain</td>
<td>Antihypertensive medications (details not mentioned)</td>
<td>Neurologic deficits resolved 2 days later CT brain changes resolved 6 weeks later</td>
</tr>
<tr>
<td>Peter et al., 2008 [26]</td>
<td>57 W</td>
<td>Metastatic colon carcinoma</td>
<td>FOLFIRI regimen + intravenous Bevacizumab</td>
<td>Cortical blindness BP 140/70 mmHg</td>
<td>Parieto-occipital subcortical lesions on MRI brain</td>
<td>No antihypertensive medications administered</td>
<td>Neurologic deficits recovered 4 weeks later MRI brain resolved 7 weeks later</td>
</tr>
<tr>
<td>Ozcan et al., 2006 [27]</td>
<td>52 W</td>
<td>Metastatic rectal adenocarcinoma</td>
<td>FOLFIRI regimen + intravenous Bevacizumab</td>
<td>Headaches, confusion, and cortical blindness BP 172/100 mmHg</td>
<td>Occipital subcortical lesions on MRI brain</td>
<td>Antihypertensive medications (details not mentioned)</td>
<td>Neurologic recovery 3 days later Radiologic resolution not mentioned</td>
</tr>
<tr>
<td>Allen et al., 2006 [28]</td>
<td>52 M</td>
<td>Metastatic rectal carcinoma</td>
<td>FOLFIIRI regimen + intravenous Bevacizumab</td>
<td>Headaches, bilateral cortical blindness, confusion, agitation, generalized tonic-clonic seizure. Systolic BP range 140–150 mmHg</td>
<td>Occipital and posterior parietal lobes subcortical lesions on MRI brain</td>
<td>Corticosteroids</td>
<td>Neurologic deficits recovered 25 days later</td>
</tr>
</tbody>
</table>

Table 1: Continued.
<table>
<thead>
<tr>
<th>Authors</th>
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<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glusker et al., 2006 [29]</td>
<td>59 W</td>
<td>Renal cancer</td>
<td>Bevacizumab</td>
<td>Severe lethargy. Blood pressure: 168/88 mmHg cortical blindness extensor plantar responses</td>
<td>Frontal and parietooccipital subcortical lesions on MRI brain</td>
<td>Lorazepam No medication for hypertension</td>
<td>Return to normal without treatment 4 days later Complete resolution of the leucoencephalopathy on MRI six weeks later</td>
</tr>
<tr>
<td>Our case</td>
<td>44 W</td>
<td>Metastatic colon cancer</td>
<td>Folfox + Bevacizumab</td>
<td>Delirium, seizures, visual disturbance, focusing signs BP: 170/90 mmHg</td>
<td>Fronto-parietooccipital lesions on brain CT</td>
<td>Intravenous nicardipine Oral phenobarbital</td>
<td>Complete neurologic recovery</td>
</tr>
</tbody>
</table>

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<tr>
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<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsunaga et al., 2012 [30]</td>
<td>43 W</td>
<td>Metastatic sigmoid cancer</td>
<td>Modified Folfox 6</td>
<td>Nausea, headache, disturbed consciousness, visual disturbance, seizures, Status epilepticus hypertension</td>
<td>Bilateral occipital lesions on MRI</td>
<td>No medication for hypertension</td>
<td>No neurologic sequelae MRI brain resolved 40 days later</td>
</tr>
<tr>
<td>Nagata et al., 2009 [31]</td>
<td>35 W</td>
<td>Metastatic sigmoid</td>
<td>Folfox regimen</td>
<td>Convulsions, headache, and visual disturbance hypertension</td>
<td>Bilateral lesions on posterior lobes on MRI</td>
<td>Antihypertensive therapy and anticonvulsive therapy</td>
<td>Complete resolution of symptoms MRI changes resolved 30 days later</td>
</tr>
<tr>
<td>Sharief and Perry, 2009 [32]</td>
<td>59 M</td>
<td>Metastatic colon cancer</td>
<td>Folfox 6 regimen</td>
<td>Status epilepticus BP: 156/98</td>
<td>Bilateral frontal cortical lesion on MRI noncontrast CT scan of the head was normal</td>
<td>Seizure medications</td>
<td>Complete recovery in 24 h MRI brain resolved two weeks later</td>
</tr>
<tr>
<td>Pinedo et al., 2007 [33]</td>
<td>62 W</td>
<td>Metastatic adenocarcinoma of rectum</td>
<td>Folfox + Bevacizumab</td>
<td>Seizures, altered mental status, bilateral lower extremity weakness BP: 190/88</td>
<td>Lesions on posterior lobes on MRI</td>
<td>Diazepam</td>
<td>Complete resolution on MRI 10 days later</td>
</tr>
<tr>
<td>Skelton et al., 2007 [34]</td>
<td>1 F</td>
<td>Metastatic adenocarcinoma of rectum</td>
<td>Folfox</td>
<td>Seizures, Altered mental status</td>
<td>Hyperintensity in the white matter of the posterior hemispheres</td>
<td></td>
<td>Resolution of lesion on repeated MRI</td>
</tr>
</tbody>
</table>
The clinical figure includes also blindness which is cortical type [4, 6, 7], nystagmus [2, 5], and cases of vomiting and nausea [8, 9]. Focusing signs have also been described [5]. Hypertension is a common sign [1, 5, 7, 8, 10, 14] but that is not always present [8, 14].

The magnetic resonance imaging (MRI) is the main test for diagnosis. It shows abnormalities signs affecting the white matter as hyperintense lesions on T2 and Flair and hypointense on T1 [1–3, 15].

In our case, MRI was not performed because our institute does not have an MRI unit, which probably delayed the diagnosis of leucoencephalopathy postchemotherapy in our patient.

This syndrome affects typically the posterior lobes (parietooccipital) [1]; that is why it is called "posterior reversible leucoencephalopathy syndrome."

In its atypical form it is also responsible for a breach of the frontal lobes (28–82%), basal ganglia (42–45%), thalamus (28–68%), brainstem (28%), and subcortical substance (5%) [2–4].

The brain CT scan may be negative in early symptoms; it might be done after the persistence of symptoms which will lead to the diagnosis by showing abnormal signs in the white matter [16]. In our patient, the brain CT scan performed one day after the onset of symptoms was normal; however, it did show the abnormalities of the white substance in the fifth day.

This syndrome is usually reversible after symptomatic treatment and after suspension of the responsible agent [1, 3], but some cases have been described as nonreversible [15].

Several cytotoxic drugs are implicated in the genesis of this syndrome. An extensive search on PubMed from January 2006 to January 2014 by looking for patients who are treated by chemotherapy containing one or more of the following drugs, Bevacizumab, Oxaliplatin, and 5 Fluorouracil, and who developed encephalopathy showed that Oxaliplatin, Bevacizumab, and in a low degree 5 FU are implicated in this syndrome. Bevacizumab is a humanized monoclonal antibody that blocks VEGFA (vascular endothelial growth factor A). Its relationship with the PRLS has been reported repeatedly in the literature. Seet and collaborator have recently published two cases of PRLS secondary to Bevacizumab; among both cases, there was a patient who also received Oxaliplatin; Bevacizumab was arrested and Oxaliplatin was continued without recurrence of PRLS [17].

Table 1 shows 14 cases of leucoencephalopathy found in patients receiving chemotherapy with Bevacizumab; in most of these cases the blood pressure was high (11/14 patients) [18–29]. The Oxaliplatin is a third generation platinum known for its toxicity on the peripheral nervous system. Search on PubMed allowed for labeling five cases of PRLS due to Oxaliplatin; among these five cases, there was a patient who has received additionally capecitabine and Bevacizumab [30–34] (Table 2). 5 FU: Its relationship with PRLS has not been clearly demonstrated in the literature. It has been described as responsible of two types of toxicity on the central nervous system: acute toxicity and delayed toxicity [35]. Acute toxicity is as an encephalopathy, which can lead to coma and cerebellar syndrome. Two mechanisms have been proposed: a deficiency in the activity of dihydropyrimidine dehydrogenase [36] and hyperammonemia [37, 38]. Delayed toxicity is a multifocal inflammatory demyelinating encephalopathy [39] and the treatment is based on corticosteroids. In our case it is difficult to decide on the drug responsible for this syndrome but it appears that the combination of several drugs of chemotherapy increases the risk of occurrence of PRLS. Practitioners have to be aware of this syndrome and must recognize it early in its typical and atypical form to set up a treatment which may allow the return to the normal state.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**


