Oxaliplatin-Induced Lhermitte Sign. A Case Report and Review of Literature

Akshay Amaraneni,1 Abhishek Seth,1 Edward A. Itawi,2 Sreenivasa R. Chandana3

Clinical Practice Points

- Oxaliplatin is a widely used chemotherapy agent in the treatment of colorectal cancer, in the adjuvant and palliative setting.
- Polyneuropathy is a common side effect of oxaliplatin at higher doses.
- Lhermitte sign is a peripheral neuropathy best characterized by an electric shock-like sensation shooting down the back into all 4 limbs when a patient’s neck is flexed.
- Oxaliplatin-induced Lhermitte sign is a very rare side effect.
- A 50-year-old Hispanic man with stage III colorectal cancer, who underwent chemotherapy with capecitabine and oxaliplatin, presented reporting that every time he bent his neck he had a severe shooting pain down both of his upper and lower extremities. Physical examination was significant for Lhermitte sign. Other causes of Lhermitte sign were ruled out.
- The clinical symptoms and Lhermitte sign completely resolved 1 year after discontinuation of oxaliplatin chemotherapy.
- The literature review indicated our case is the first report of Lhermitte sign induced by oxaliplatin in combination with capecitabine in colorectal cancer.

Introduction

Lhermitte sign is a neurologic disorder that is best characterized by an electric shock sensation that radiates distally through all 4 extremities when a patient flexes their neck. This entity was first described during the First World War in 1917 but was only brought to the neurology literature in 1924 when Jean Lhermitte published a case with this entity in a patient with multiple sclerosis.1 Lhermitte sign is most commonly seen in patients with multiple sclerosis.2 It can also be seen in patients with a history of radiation therapy (mostly to spinal and head and neck cancers), chemotherapy,1 herpes zoster,3 Behcet disease,4 systemic lupus erythematosus,5 spinal cord trauma,6 and subacute combined degeneration secondary to vitamin B12 deficiency.7 Here we report a case of Lhermitte sign induced by oxaliplatin, in a patient with locally advanced colorectal cancer.

Case Report

Our patient was a 50-year-old Hispanic male. He had no significant medical history and underwent a routine screening colonoscopy. Social history was significant for 30 pack-year smoking and 1 beer per day of alcohol consumption. He quit smoking approximately 10 years previously. He was a welder by profession. He denied any family history of colon cancer. His paternal grandmother died of acute leukemia in her 70s. He reported no medication or food allergies. He did not take any prescription medications. The colonoscopy procedure revealed a 5-mm polyp at 30 cm and a small ulcerated mass at the rectosigmoid junction, 15 cm from the anal verge. The patient also underwent a snare polypectomy and biopsy of a rectosigmoid mass/tumor. Pathology revealed invasive low-grade adenocarcinoma in the rectosigmoid biopsy and tubular adenoma in the polyp. Subsequently, the patient was referred to a colorectal surgeon. A computerized tomography scan of the chest, abdomen, and pelvis revealed an asymmetric wall thickening at the rectosigmoid junction, along with diverticulosis. There was no clinical evidence for lymph node
or visceral metastasis. Because of the location of the tumor, the patient underwent a laparoscopic low anterior resection, with end to end anastomosis. Pathology revealed a low-grade adenocarcinoma at the rectosigmoid junction, with invasion into adventitial fat. Margins were widely negative for cancer. Three of 12 regional lymph nodes were positive for adenocarcinoma. Estimated tumor size was 2 × 6 × 0.8 cm. There were suspected to be foci of angiolymphatic invasion. There was no evidence for the loss of the mismatch repair proteins according to immunohistochemistry. His clinical staging was stage III (T3N1bM0). As per National Comprehensive Cancer Network guidelines, 6-month adjuvant chemotherapy with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) was recommended. Because the tumor was located at the rectosigmoid junction with widely negative margins and relatively good risk features, radiation was not considered as part of the adjuvant therapy. Because of the patient’s busy work schedule and request, an informed decision was made to treat him with a CAPEOX (capecitabine and oxaliplatin) regimen. The oral capecitabine dose was 1500 mg (1000 mg/m²) twice daily with a 2 weeks on, 1 week off schedule. Oxaliplatin was given intravenously at a dose of 130 mg/m², once every 3 weeks. The FOLFOX regimen uses 85 mg/m² of oxaliplatin every 2 weeks as opposed to the CAPEOX regimen, which uses 130 mg/m² of oxaliplatin every 3 weeks. After 7 cycles of chemotherapy (with a cumulative oxaliplatin dose of 830 mg/m²), the patient presented with severe sensory and numbness in his upper extremities and at his fingertips. A thorough history and physical examination revealed a classic Lhermitte sign on neck flexion, with no other significant findings. Complete blood counts revealed macrocytosis, with normal hemoglobin. Red blood cell folate, methylmalonic acid, erythrocyte folate, and vitamin B12 were normal. Thyroid stimulating hormone, antinuclear antigen, and magnesium levels were within normal limits. A magnetic resonance imaging scan of the spine with and without gadolinium contrast did not reveal any evidence for metastatic disease or demyelination process. Electromyographic examination and somatosensory evoked potentials were not performed. An informed decision was made to discontinue oxaliplatin. Capecitabine was continued to complete a total of 6 months of adjuvant chemotherapy. Six months after discontinuation of oxaliplatin, his symptoms completely resolved, including upper extremity paresthesia. A repeat computed tomography scan and 1-year follow-up colonoscopy did not reveal any evidence for recurrent colon cancer.

### Discussion

Lhermitte phenomenon due to chemotherapy is rare. Its onset might be delayed by weeks to months, with the most common chemotherapy culprit being cisplatin and oxaliplatin.10-12 Lhermitte phenomenon has been reported in regimens that have included cyclophosphamide13 and fludarabine.14 During our literature search, we identified 13 reported cases of oxaliplatin-associated Lhermitte sign (Table 1).10,11,15 Interestingly, all of these patients received oxaliplatin along with 5-fluorouracil. The cumulative dose of oxaliplatin ranged between 574 mg and 2040 mg. There was no sex predilection. Lhermitte sign was also associated with paresthesias. In most patients, Lhermitte sign symptoms persisted for approximately 3 to 6 months. Ciucci et al12 reported Lhermitte sign in a patient with ovarian cancer, who was pretreated with cisplatin. Interestingly, the cumulative dose of oxaliplatin was 450 mg/m². Docetaxel has also been reported in association with Lhermitte sign. Transient Lhermitte sign was reported in 5 of 87 patients treated with docetaxel.15 Multifocal central nervous system demyelination and Lhermitte phenomenon was also reported in a patient with chronic leukemia treated with a fludarabine-based chemotherapy regimen. In most of these patients, Lhermitte sign resolved after discontinuation of chemotherapy.14 Interestingly, there were no reported cases of Lhermitte sign in the clinical trials involving oxaliplatin.17 Although this can be a debilitating condition, it seems to be almost fully reversible with few, if any, residual paresthesias.

### Table 1: Thirteen Reported Cases of Oxaliplatin-Associated Lhermitte Sign

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Age, Years/Sex</th>
<th>Treatment Regimen</th>
<th>Underlying Disease</th>
<th>Cumulative Dose of Oxaliplatin</th>
<th>Length of Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al, 2009</td>
<td>65/M</td>
<td>FOLFOX-4</td>
<td>Stage IV colon cancer</td>
<td>897 mg/m²</td>
<td>17 Months</td>
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<tr>
<td></td>
<td>50/M</td>
<td>CAPEOX</td>
<td>Stage III colorectal cancer</td>
<td>830 mg/m²</td>
<td>6 Months</td>
</tr>
<tr>
<td>28/M</td>
<td>FOLFOX-6</td>
<td></td>
<td>Stage IV colon cancer</td>
<td>1100 mg/m²</td>
<td>7 Months</td>
</tr>
<tr>
<td>62/M</td>
<td>FOLFOX-6</td>
<td></td>
<td>Stage IV rectal cancer</td>
<td>894 mg/m²</td>
<td>6 Months</td>
</tr>
<tr>
<td>72/F</td>
<td>FOLFOX-4</td>
<td></td>
<td>Stage IIIC colon cancer</td>
<td>574 mg/m²</td>
<td>3-6 Months</td>
</tr>
<tr>
<td>73/F</td>
<td>FOLFOX-6</td>
<td></td>
<td>Stage IV colon cancer</td>
<td>840 mg/m²</td>
<td>Unresolved at death (6 months)</td>
</tr>
<tr>
<td>Jurado et al, 2008</td>
<td>33/F</td>
<td>FOLFOX-4</td>
<td>Stage IV colon cancer</td>
<td>765 mg/m²</td>
<td>2 Months</td>
</tr>
<tr>
<td></td>
<td>53/F</td>
<td>FOLFOX-4</td>
<td>Stage IV colon cancer</td>
<td>860 mg/m²</td>
<td>4 Months</td>
</tr>
<tr>
<td></td>
<td>54/F</td>
<td>FOLFOX-4</td>
<td>Stage III colon cancer</td>
<td>680 mg/m²</td>
<td>11 Months</td>
</tr>
<tr>
<td>Taieb et al, 2002</td>
<td>59/F</td>
<td>FOLFOX-4</td>
<td>Stage IV colon cancer</td>
<td>1248 mg/m²</td>
<td>Unresolved at death (3 months)</td>
</tr>
<tr>
<td></td>
<td>50/M</td>
<td>FOLFOX-4</td>
<td>Stage IV colon cancer</td>
<td>1465 mg/m²</td>
<td>5 Months</td>
</tr>
<tr>
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<td>52/M</td>
<td>FOLFOX-4</td>
<td>Stage IV colon cancer</td>
<td>2040 mg/m²</td>
<td>4 Months</td>
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<tr>
<td></td>
<td>57/F</td>
<td>FOLFOX-4</td>
<td>Stage IV colon cancer</td>
<td>1596 mg/m²</td>
<td>3 Months</td>
</tr>
<tr>
<td>Our Case, 2014</td>
<td>50/M</td>
<td>CAPEOX</td>
<td>Stage III colorectal cancer</td>
<td>830 mg/m²</td>
<td>6 Months</td>
</tr>
</tbody>
</table>

Abbreviations: CAPEOX = Capecitabine and Oxaliplatin; F = female; FOLFOX = Folinic Acid, 5-Fluorouracil and Oxaliplatin; M = male.
Pathophysiology for oxaliplatin-induced neuropathy is under investigation. In general, chemotherapy-induced peripheral neuropathy is a chronic disorder characterized by paresthesias and dysesthesias including numbness, tingling, burning sensations, and lack of sensation in the extremities. Research in animal models suggest possible injury to microglia, astrocytes, or the microenvironment involving proinflammatory signals in the spinal cord could cause chemotherapy-induced peripheral neuropathy. A recent report by Robinson et al suggests that the activation of astrocytes modulate an inflammatory response through the release of proinflammatory cytokines during oxaliplatin-induced peripheral neuropathy.

To our knowledge, we are reporting the first case of Lhermitte sign induced by oxaliplatin in a Hispanic patient with colorectal cancer concurrently being treated with capecitabine. He successfully completed chemotherapy with capecitabine after discontinuation of oxaliplatin. The patient’s symptoms subsided after discontinuation of oxaliplatin and completely resolved within 6 months. This is in accordance with other described cases in the literature. Our patient had a cumulative oxaliplatin dose of 830 mg/m². Historically, the dose of oxaliplatin received by our patient was less than in several reported cases. This leads us to believe there might be an additional mechanism involved in the process, including greater interval dosing (130 mg/m²) and/or coadministration with capecitabine. It is not clear whether capecitabine could have a role in causing or potentiating the risk of developing Lhermitte sign. There is also a possibility of genetic variation of the proteins responsible for metabolizing oxaliplatin in our patient that would make him susceptible to developing Lhermitte sign.

**Conclusion**

Oxaliplatin is one of the most widely used chemotherapeutic agents. Although the side effect profile of oxaliplatin is improved with better supportive care, rare side effects such as Lhermitte sign cannot be ignored. In our patient, the concurrent treatment with capecitabine might have had an underlying role in sensitizing the patient and making him more prone to developing Lhermitte sign. At this time it is not known if there is an association of capecitabine with Lhermitte sign. Because capecitabine is being used more frequently instead of 5-fluorouracil, in combination with oxaliplatin in colorectal cancer, neurological side effects including Lhermitte sign could happen more frequently. Because oxaliplatin-induced Lhermitte sign seems to be a reversible side effect, medical oncologists should pay close attention to this side effect and stop the oxaliplatin chemotherapy in the appropriate setting.

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**Disclosure**

Authors do not have any conflicts of interest to disclose.

**References**