Guillain-Barré syndrome in a patient with metastatic colon cancer receiving oxaliplatin-based chemotherapy

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We report Guillain-Barré syndrome (GBS), developed in a patient with metastatic colon cancer, receiving oxaliplatin-based chemotherapy. The 53-year-old patient was treated with first-line chemotherapy consisting of oxaliplatin 45 mg/m^2, 5-fluorouracil 450 mg/m^2 and folinic acid 200 mg/m^2, all given on the same day in a weekly schedule. After 13 weeks of treatment and a cumulative oxaliplatin dose of 585 mg/m^2, the patient developed unsteadiness of gait, dysphagia, and weakness of both the upper and lower limbs, as well as impairment of all sensory modalities. Clinical examination, computed tomography and magnetic resonance imaging scans of the brain, blood tests, nerve conduction studies, and cerebrospinal fluid analysis confirmed the diagnosis of GBS. Intravenous immunoglobulin G was administered for 5 days and the patient recovered fully. Oxaliplatin can cause acute and delayed neurotoxicity, but this is the first report of GBS in a patient receiving oxaliplatin-based chemotherapy. Elevation of pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, induced by oxaliplatin, may represent the relevant causal links involved in the cascade of events which have led to the immune-mediated demyelination in the peripheral nervous system in this patient. *Anti-Cancer Drugs* 15:997–999 © 2004 Lippincott Williams & Wilkins.

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Case report

This 53-year-old male patient, with unremarkable past medical history, underwent right hemicolectomy for adenocarcinoma of the ascending colon, stage Duke's C, in October 2001. He received adjuvant chemotherapy with CPT-11 80 mg/m^2, 5-fluorouracil 450 mg/m^2 and folinic acid 200 mg/m^2, all given on the same day weekly for 6 consecutive weeks followed by a 2-week rest. Four cycles of the above regimen had been planned.

Three months later, CEA raised to 325 U/l, and a computed tomography (CT) scan of the abdomen and pelvis showed three hypodense lesions of the liver, compatible with metastases. A magnetic resonance imaging (MRI) scan of the liver confirmed six hepatic metastases. First-line chemotherapy for metastatic disease was then initiated with oxaliplatin 45 mg/m^2, 5-fluorouracil 450 mg/m^2 and folinic acid 200 mg/m^2, all given on the same day weekly for 6 consecutive weeks followed by a 2-week rest. The patient was re-evaluated after having received 2 cycles of the above regimen. He had shown a minor response, as assessed with CT and MRI scans, while CEA fell to 59 U/l.

The treatment had been initially very well tolerated, but after the first week of the third cycle he developed paresthesias of the upper and lower limbs, followed 1 week later by unsteadiness of gait, dysphagia, and weakness of both the upper and lower limbs. On neurological examination he exhibited peripheral facial diplegia, proximal greater than distal weakness of the upper and lower limbs, as well as stocking-glove impairment of all sensory modalities. He was able to stand and walk only on a widened base. The ankle jerks were reduced, while the knee jerks were absent bilaterally. Full blood count, glucose, urea, creatinine, aminotransferases, bilirubin, sodium, potassium, calcium, PT, INR and APTT were all within the normal range. Both CT and gadolinium-enhanced MRI scans of the brain were normal. Nerve conduction studies revealed considerable reduction (more than 40% of the normal mean) of the motor velocity of the median nerve bilaterally and right ulnar nerve (across the sulcus), with significant prolongation of the distal latencies of the median nerve bilaterally and right peroneal nerve. Sensory conduction was significantly slowed in most nerves of both the upper and lower limbs. The results of nerve conduction studies are summarized in Table 1. Electromyography of the weak muscles showed no spontaneous fibrillations or positive sharp waves. Motor unit recruitment was reduced.

An elevated cerebrospinal fluid (CSF) protein of 1.85 g/l was found, while the CSF cell count was normal (2/mm^3). Guillain-Barré syndrome (GBS) was diagnosed and he was

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Table 1 Nerve conduction studies

Nerve	Right	Left
Common peroneal		
DML (ms)	6.8 (3.7 ± 0.6)	ND
distal CMAP (mV)	3.5 (9.0 ± 5.2)	ND
MCV (m/s)	46 (47.5 ± 4.0)	ND
Sural		
SNAP (iV)	12 (16 ± 8.4)	10
SCV (m/s)	32 (53.4 ± 5.5)	34
Median		
DML (ms)	22 (2.8 ± 0.4)	11
distal CMAP (mV)	0.7 (12.5 ± 6.5)	0.7
MCV (m/s)	30 (58.6 ± 4.5)	30
SNAP (iV)	18 (28 ± 14.2)	ND
SCV (m/s)	38 (58.5 ± 5.4)	ND
Ulnar		
DML (ms)	3.3 (2.1 ± 0.3)	3.5
distal CMAP (mV)	3.9, 1.3[a] (10.5 ± 3.7)	2.5
MCV (m/s)	47, 27[a] (60.3 ± 5.7)	44
SNAP (iV)	14 (20.7 ± 16.5)	16
SCV (m/s)	40 (57.5 ± 5.2)	43

DML, distal motor latency; CMAP, compound muscle action potential; MCV, motor conduction velocity; SNAP, sensory nerve action potential; SCV, sensory conduction velocity; ND, not done.
[a]Conduction block across the sulcus of the right ulnar nerve with 65% reduction of the MAP when elicited by proximal stimulation.

treated with i.v. immunoglobulin G (IVIg, 40 g i.v./day for 5 days).

The patient then showed remarkable recovery. One week later, the only symptom he complained of was mild paresthesias of the upper and lower limbs. The physical examination was normal with no motor or sensory abnormalities. Oxaliplatin was discontinued.

Discussion

To the best of our knowledge this is the first report of GBS in a patient receiving oxaliplatin-based chemotherapy. GBS is an acute inflammatory demyelinating neuropathy characterized by acute onset of peripheral and cranial nerve dysfunction. Viral respiratory or gastrointestinal infection, immunization or surgery often precedes neurologic symptoms by 5 days to 3 weeks. Notably, our patient did not give a history of antecedent acute infectious illness. Symptoms and signs include rapidly progressive symmetric weakness, loss of tendon reflexes, facial diplegia, oropharyngeal and respiratory paresis, and impaired sensation in the hands and feet. The condition worsened for several days to 3 weeks, followed by a period of stability and then gradual improvement to normal or nearly normal function. Early plasmapheresis or IVIg accelerates recovery and diminishes the incidence of long-term neurologic disability. Nerve conduction velocities are often reduced. Distal sensory and motor latencies are prolonged. Histologically, GBS is characterized by focal segmental demyelination with perivascular and endoneurial infiltrates of lymphocytes and monocytes or macrophages. The CSF protein content is elevated in most patients with GBS, but may be normal in the first few days after onset [1].

Neurotoxicity is the most frequent dose-limiting toxicity of oxaliplatin. Two types of neurotoxicity have been described so far: acute and delayed [2]. Acute neurotoxicity is characterized by the rapid onset of cold-induced distal dysesthesia and/or paresthesia. Sensory symptoms may be accompanied by cold-depended muscular contractions of the extremities or the jaw. The symptoms occurring during or shortly after infusion are usually transient and mild [2]. Studies have shown patients with acute sensory symptoms to display little or no axonal degeneration, suggesting a specific effect of oxaliplatin on sensory neurons and/or motor neurons or muscle cells that is not observed with other platinum agents. Nerve biopsies have not shown any meaningful changes in neuronal morphology. Similarly, electron microscopy showed the overall unmyelinated fiber density to remain intact. The similarity of the acute symptoms induced by oxaliplatin with those caused by several drugs or toxins acting on neuronal or muscular ion channels suggests that these symptoms may result from a specific interaction of oxaliplatin with ion channels located in the cellular membrane [3,4].

Delayed neurotoxicity includes a persistent sensory peripheral neuropathy, which develops after prolonged treatment. This is a cumulative toxicity causing superficial and deep sensory loss, sensory ataxia, and functional impairment.

The dose-limiting sensory neuropathy observed as a consequence of oxaliplatin-induced cumulative neurotoxicity develops progressively in approximately 10–15% of patients after a total oxaliplatin dose of 780–850 mg/m^2. It occurs less frequently than with cisplatin and patients are more likely to recover after the treatment is stopped [5]. The mechanism of cumulative neurotoxicity remains unknown; however, it is likely that oxaliplatin, as with other platinum compounds, may be toxic to dorsal root ganglion cells by inducing re-entry into the cell cycle, which, in terminally differentiated sensory neurons, leads to apoptosis [6].

Our patient developed GBS syndrome after a cumulative oxaliplatin dose of 585 mg/m^2. His symptoms developed gradually several days after the last oxaliplatin infusion, deteriorating steadily over a time period of approximately 2 weeks. GBS cannot be classified according to the types of neurotoxicity which have so far been described with oxaliplatin. However, since oxaliplatin is a relatively novel chemotherapeutic compound, it may be possible that other types and mechanisms of neurotoxicity exist, which are not common and have not been recognized. It has been shown recently that oxaliplatin can induce elevation

of various cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, in serum [7,8]. These pro-inflammatory cytokines represent relevant signals involved in the cascade of events leading to the immune-mediated demyelination in the peripheral nervous system [9]. TNF-α levels correlate with disease severity in GBS [10], while IL-6 is augmented systematically early in GBS [11]. These hypothetical events may have been triggered because our patient received a weekly administered regimen. Usually, oxaliplatin is given either every 3 weeks at a dose of 130 mg/m^2 or every 2 weeks at 85 mg/m^2. Still, the rapid resolution of the neurological symptoms after IVIg treatment raises the possibility that the mechanism underlying the appearance of GBS in this particular patient may have not included macrophage-mediated demyelination of the peripheral nervous system. Alternatively, anti-myelin antibodies may have interfered with ion channels in the cell membrane, just as it is believed to be the case in multifocal motor neuropathy with conduction blocks [12].

Although most patients with GBS have no identifiable infection preceding the symptoms, it has been increasingly recognized that mainly an antecedent *Campylobacter jejuni* infection may contribute to disease development and we cannot exclude the remote possibility that the GBS in this patient may be due simply to an infectious agent. However, patients with *C. jejuni* infections are more likely than others to have neurophysiological criteria of axonal neuropathy and more severe outcome. Similarly, cytomegalovirus infection has been associated with severe disease and prominent sensory involvement. Furthermore, there is reason to believe that the infectious agent has in any case to interact with additional host factors [13].

GBS has been rarely described in patients with co-morbid malignancies, mainly lymphomas, and it may be argued that our patient could represent such a case of 'paraneoplastic' GBS. However, in a large series of 435 GBS patients, only nine were identified to have malignancies, slightly more than the incidence rate of cancer in the same region would predict [14]. None of them had colon cancer. So far, it has not been possible to define criteria for paraneoplastic disease for patients with malignancies and GBS (i.e. such as for paraneoplastic gaglionitis). In our patient the two diseases had a definitely independent progression.

In conclusion, we believe that our patient developed GBS as a result of treatment with oxaliplatin. With the new accelerated approval mechanisms for novel compounds in oncology, we should be alert to recognize adverse events that have not been described in the initial studies.

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