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Rare Case of Motor Neuropathy with 5-Fluorouracil Chemotherapy: A Case Report

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Abstract. Peripheral neuropathy is a known side effect of chemotherapy. 5-Fluorouracil is used in treating patients with colon cancer. Literature review reported peripheral neuropathy rarely used with 5-Fluorouracil. All cases described sensory neuropathy and demyelinating nerve injury. A 69-year-old female developed a predominantly motor neuropathy following treatment with 5-Fluorouracil for advanced colorectal cancer. Electrophysiological study indicated axonal injury. Fortunately, the patient recovered her motor functions completely. She declined using further chemotherapy in the future. To date, this is the first reported case of motor peripheral neuropathy with 5-Fluorouracil exposure as no other explanations could be found. In colorectal cancer patients receiving 5-Fluorouracil containing chemotherapy and presenting with motor neuropathy, induced toxicity should be considered if other causes are ruled out.

Keywords: 5-Fluorouracil, Neurological toxicity, Peripheral neuropathy, Axonal injury.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and second in females[1]. In 2010, CRC accounts for 9% of all cancer deaths in United States[2].

5-Fluorouracil (5-FU) is the main backbone of chemotherapy treatment in CRC. It is administered in different ways including bolus or continuous infusion. Gastrointestinal and hematological toxicities are the

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most common side effect with 5-FU. Neurological complications are less common with 5-FU use. The most characteristic complication is multifocal cerebellar demyelination[3]. Patients will develop clinical findings of cerebellar dysfunction including weakness, ataxia and loss of coordination. The cerebellar dysfunction is related to a central demyelinating process involving the cerebellum. Other neurological complications include encephalopathy and rarely optic neuropathy, focal dystonia, Parkinson syndrome and peripheral neuropathy[4-8]. Few cases of peripheral neuropathy have been reported in the literature and described sensory neuropathy.

Axonal polyneuropathy is the most common type of polyneuropathy affecting patient treated with chemotherapy. It is caused by damage to the axon transport system for cellular constituents leading to significant axon dysfunction. It usually starts involving small distal fibers and progress to involve larger proximal fibers after. This progression produces the characteristic distal-to-proximal pattern of symptoms. Axonal neuropathy is the most common response of neurons to metabolic and toxic disturbances. Platinum, Vinca alkaloids and taxanes are among the most common cause for axonal neuropathy.

Case

A 69-year-old woman presented to emergency room with abdominal pain. She had experienced alternating constipation and diarrhea for two years. She was worked up in the past with normal colonoscopy and negative blood in the stool. Her tests showed diverticular disease. The pain had worsened over the past two weeks. The patient underwent an emergency abdominal computerized tomography (CT) scan which revealed a mass in the sigmoid colon invading the vagina and bladder. Colonoscopy was done and showed a mass in the sigmoid colon which was biopsied and revealed a poorly differentiated adenocarcinoma of colonic origin. Metastatic work up showed a small lymph node measuring 7 mm in the mesentery and no evidence of distant metastasis.

The patient was referred to the cancer centre for consideration of neoadjuvant treatment to down size the tumor and facilitate curative surgery.

The past medical history was positive for diverticular disease and gastroesophageal reflux disease. There was no history of diabetes or neurological abnormalities.

After meeting her medical and radiation oncologist, the patient agreed to begin a combined treatment of chemotherapy and radiation, followed by surgery and adjuvant chemotherapy. The combined treatment consisted of five and a half weeks of continuous 5-FU infusion (225 mg/m^2) with daily radiation. This protocol was extrapolated from treating patient with locally advanced rectal cancer. The patient received her planned treatment without any interruption or dose reduction. The surgery was scheduled for six to eight weeks after finishing the combined treatment.

Ten days after completing treatment, the patient developed bilateral myalgia in both calf muscles associated with bilateral leg weakness. There was no sensory deficit or bulbar symptoms. The pain lessened with pain medication. However, the weakness progressed to involve both upper limbs. The patient experienced difficulty walking upstairs and hanging her coat. Over time, she was unable to open jars and had difficulty holding a cup in her hands.

At this time, she reported to the cancer clinic and was seen on the same day. An urgent neurological opinion was obtained.

The neurological examination showed mild (4) weakness of upper and lower limbs. The tone was normal throughout the arms and legs. Reflexes were 2 throughout the arms and symmetrical. In the legs, the reflexes were 2 at the patellae and symmetrical, 1 at the right Achilles and 0 at the left Achilles. The left toe was down going and the right was mute. She had a slight decrease in vibration with normal pinprick, position and fine touch. Muscle coordination and cerebellar examination were normal.

The electrophysiologic study revealed a predominately motor axonal injury. There was no evidence of myopathy, neuromuscular defects or demyelinating disease. The motor amplitude of the left median nerve was reduced to 3.7 mV with normal terminal latency and conduction velocity. The motor amplitude of the left ulnar nerve was 5.4 mV with normal latency and conduction velocity. Left ulnar motor study to FDI showed reduced response at 5.9 mV with normal conduction velocity. The left deep peroneal motor study to extensor digitorum brevis (EDB) was reduced at 0.8 mV with normal conduction velocity. The left tibial motor study was reduced at 4.7 mV with normal conduction velocity. The left common peroneal motor study to anterolateral group was

reduced at 2.8 mV with normal conduction velocity. Sensory studies were normal at the left median, radial, ulnar nerves and slightly reduced at the superficial peroneal nerve at 3 micro volts. (Table. 1) The left tibial F response was of normal latency. The left tibial H response was absent. Needle examination of the left tibialis anterior, medial gastrocnemius, vastus medialis and iliopsoas revealed normal activity with normal motor unit morphology and recruitment. Biceps, deltoid and mid-thoracic paraspinals showed normal spontaneous activity. The patient declined to have lumbar puncture. Computerized tomography (CT) and magnetic resonance imaging (MRI) of the brain and spine did not reveal any evidence of metastasis or cord compression. It was difficult to localize her disease. However, no evidence of upper motor disease and the electrophysiologic study supported distal more than proximal predominantly motor disease. The clinical examination and neuromuscular studies favoured the involvement of the peripheral nerves.

Table 1. Comparison of electrophysiologic study at diagnosis and four months later.

	At Presentation	Four Months Later
Motor Study		
Median Nerve (mV)	3.7	5.3
Tibial Nerve (mV)	4.7	5.7
Deep Peroneal Nerve (mV)	0.8	3.3
Common Peroneal Nerve (mV)	2.8	4.7
Sensory Study		
Superficial Peroneal Nerve (Microvolt)	3	5

The surgery was deferred for an additional 3 weeks. The patient had significant response to treatment, and an abdominoperineal resection with partial vaginectomy and cystectomy was performed. Postoperatively, the patient continued to recover well. She refused to receive further chemotherapy given the significant morbidity she had experienced earlier.

The weakness continued to improve and two months later the patient had completely recovered. The electrophysiologic study was repeated and showed significant improvement. The left median nerve motor amplitude was 5.3 mV with normal conduction velocity and terminal latency (previously 3.7 mV). The left deep peroneal nerve motor amplitude was 3.3 mV with normal conduction velocity and latency (previously 0.8mV). The left tibial motor study was 5.7 mV with normal conduction velocity and latency (previously 4.7 mV). The left common

peroneal motor study was 4.7 mV with normal conduction velocity (previously 2.8 mV). The left tibial H response was prolonged at 35.2 msec. The sensory study showed improvement in the lower limbs with amplitude of 5 micro volts in the left sural and sensory peroneal nerve (previously 3.2 micro volts). The sensory study of upper limb was essentially normal (Table 1). The needle electromyography (EMG) studies on the left side showed mild denervation on the lower extremity nerve conduction study. Otherwise, motor units were essentially normal, with some occasional large units to tibialis anterior and first dorsal interosseous. This follow up study revealed an improvement following a length dependent pattern of this patient's predominantly motor axonal neuropathy. The motor studies showed greater improvement than the sensory studies.

The patient is on surveillance with no evidence of cancer recurrence or neurological complaints.

Discussion

This patient represents an unusual neurological side effect of 5-FU use. From reviewing the literature, the incidence of neurological toxicity in patients receiving high dose 5-FU chemotherapy (2600 mg/m^2) is estimated 5.7%[6]. The mechanism by which 5-FU induces neurological toxicity is not fully understood. One of the proposed mechanisms is the accumulation of the drug in patients with Dihydropyrimidine dehydrogenase (DPD) deficiency[9]. Approximately 85% of 5-FU is degraded by DPD. Patients with DPD deficiency present with severe side effects including myelosuppression, mucositis and hand-foot syndrome. Likewise, those patients may develop severe neurological toxicity. The other suggested mechanism is the accumulation of the final product of 5-FU including monofluoroacetic acid and alpha fluoro-beta-alanine (FBAL) that could have direct toxicity on myelin itself[10]. In previous reported cases of 5-FU induced neurological toxicity, the evaluation of patients with multifocal cerebellar dysfunction revealed a demyelinating process[6]. In patients with 5-FU induced peripheral neuropathy, the electrophysiologic study revealed demyelinating injury[8]. In patients presenting with 5-FU induced encephalopathy, electroencephalogram (EEG) revealed diffuse cortical dysfunction with diffuse slow waves or intermittent theta waves suggesting metabolic or toxic encephalopathy[11]. Furthermore, the blood test revealed

hyperammonemia and elevated lactic acid[11]. Peripheral neuropathy was rarely reported and it has been described as predominately sensory neuropathy. Stein *et al.*[8] reported two cases of sensory neuropathy in patient receiving 5-FU alone. Both patients developed demyelinating neuropathy and their symptoms stabilized after discontinuation of 5-FU; and one of them deteriorated after resuming 5-FU infusion[8]. In this case report, the patient developed predominately motor neuropathy and the electrophysiologic study revealed an axonal injury without any evidence of demyelination and normal nerve conduction velocity. These findings are unique in that; it has never been reported in the past and might suggest a different mechanism of 5-FU induced neurological toxicity**.** Yeh and Cheng developed diagnostic criteria for 5-FU induced acute neurological toxicity[11]. It includes: (I) Development of encephalopathy during or shortly after completion of 5-FU administration; (II) exclusion of other metabolic causes that may affect consciousness and mental functioning and (III) exclusion of an adverse effect by concomitant medication. These criteria have been developed to diagnose 5-FU induced encephalopathy. Patients with 5-FU toxicity recover well[6]. Majority of reported case described complete recovery without any intervention[9,11]. In single report, a patient with esophageal carcinoma presented with encephalopathy and cerebellar ataxia; the encephalopathy recovered within 72 hours however, the cerebellar ataxia became permanent[12]. Thymidine infusion was used in patients with severe encephalopathy and shown to enhance faster recovery[8]. Given the rarity and the rapid recovery of peripheral neuropathy with 5-FU, thymidine infusion has never been used in these patients.

In this case, the patient regained her motor functions and the electrophysiologic study revealed complete recovery. She did not have any risk factor for peripheral neuropathy and no other concomitant drug use to explain her motor neuropathy apart from 5-FU use. Despite her recovery, she declined restarting her adjuvant chemotherapy after her surgery.

Conclusion

In patients receiving 5-FU chemotherapy and presenting with motor neuropathy, 5-FU induced neurotoxicity should be considered if other causes are ruled out. Reporting similar cases in the future by medical

oncologist and neurologist will be helpful to understand the mechanism of this form of neurotoxicity.

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حالة نادرة من التهاب الأعصاب الطرفي الحركي ناتج عن العلاج الكيميائي 5-Fluorouracil

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المستخلص. التهاب الأعصاب الطرفي هو من الأعراض الجانبية المعروفة الناتجة عن استخدام العلاجات الكيميائية لمرضى السرطان. ومن أشهر العلاجات الكيميائية المستخدمة في علاج المرضى المصابين بسرطان الأمعاء الغليظة دواء 5-Fluorouracil. وبحسب الوارد في المنشورات الطبية فإنه من النادر الإصابة بالتهاب الأعصاب الطرفي كنتيجة لاستخدام هذا العلاج. في حال حصول هذه المضاعفات فإن المرضى يصابون بلتهاب الأعصاب الطرفي الحسي نتيجة لتلف غشاء المايلين (Demyelination). هذا التقرير يصف حالة مريضة تبلغ من العمر تسعة وستين عاما عولجت باستخدام العلاج الكيميائي 5-Fluorouracil لسرطان ذو مرحلة متقدمة في الأمعاء الغليظة ، وقد أصيبت المريضة بالتهاب الأعصاب الطرفي الحركي كنتيجةلاستخدام العلاج الكيميائي5-Fluorouracil. أظهرت الفحوصات الكهروعضوية Electrophysiology حصول تلف في محور العصبون (Axonal injury) . وبعد مرور شهرين من إيقاف العلاج، استعادت المريضة وظائفها الحركية الطبيعية كاملة وبالرغم من ذلك فإنها رفضت إتمام الجرعات المتبقية من العلاج الكيميائي لاحتوائها على نفس الدواء. تمثل هذه الحاله أول تقرير يصف التهاب الأعصاب الطرفي الحركي كعرض جانبي لاستخدام الدواء الكيميائي5-Fluorouracil. ولذلك فإنه

يجب إدراج العلاج الكيميائي 5-Fluorouracil كأحد مسببات التهاب الأعصاب الطرفي الحركي بعد استبعاد المسببات الأخرى والأكثر شيوعآ.