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Platinum and Taxane Induced Common Peroneal Nerve Palsy (Foot Drop): Case Series and Review of the Literature

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Abstract

Chemotherapy Induced Peripheral Neurotoxicity (CIPN) is an adverse event seen in patients being treated with a number of chemotherapeutic classes of drugs such as taxanes and platinum among others. Presentation can vary from mild paresthesia and dysesthesia to debilitating pain often leading to dose reduction, delay or discontinuation of therapy. The common peroneal nerve is a peripheral nerve that arises from the sciatic nerve. Foot drop is the result of peroneal nerve palsy. This is commonly seen due to injury to the nerve at the level of the fibular neck. The mechanism of injury may be due to compression of the nerve from prolonged lying or direct injury.

Though rare, foot drop can be a manifestation of central nervous system pathology. Cerebrovascular accidents and space occupying lesions involving the brain or the spine causing foot drop have been reported. There are few mentions in the literature of foot drop related to neurotoxic chemotherapeutic agents.

Here we describe five cases of chemotherapy associated isolated peroneal nerve paresis resulting in foot drop after several cycles with platinum and/or taxanes. We postulate that chemotherapeutic agents contributed to peroneal nerve palsy in all the five cases. In all of these cases, no other plausible explanation was found for the foot drop. All patients who continued follow up showed complete recovery of motor function on discontinuation of offending agents and supportive treatment. To our knowledge, platinum and taxane induced isolated common peroneal neuropathy has not been widely reported.

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Introduction

Chemotherapy Induced Peripheral Neurotoxicity (CIPN) is an adverse event seen in patients being treated with a number of chemotherapeutic classes of drugs such as taxanes, vinca alkaloids and platinum among others. Presentation can vary from mild paresthesia and dysesthesia to debilitating pain often leading to dose reduction, delay or discontinuation of therapy. In clinical practice, a majority of these patients present with sensory symptoms. Motor and autonomic symptoms are less frequent and usually milder [1].

The common peroneal nerve is a peripheral nerve that arises from the sciatic nerve. Its branches provide motor innervation to the muscles responsible for dorsiflexion and eversion as well as sensory innervation of the skin over the upper lateral third of the foot. Foot drop is the result of peroneal nerve palsy. This is commonly seen due to injury to the nerve at the level of the fibular neck [2]. The mechanism of injury may be due to compression of the nerve from prolonged lying or direct injury. Severe weight loss has also been hypothesized as a cause of peroneal nerve injury [3].

Though rare, foot drop can be a manifestation of central nervous system pathology [4]. Cerebrovascular accidents and space occupying lesions involving the brain [5-11] or the spine [12] causing foot drop have been reported. Other rare causes include multiple sclerosis, hemorrhagic contusion from gunshot wound [7], head trauma, neurocysticercosis [10] and brain abscess. Due to the involvement of the upper motor neurons of the parasagittal motor cortex, these patients tend to present with spastic foot drop, usually associated with other neurological signs such as hyperreflexia, clonus and a positive Babinski reflex [5]. There are few mentions in the literature of foot drop related to neurotoxic chemotherapeutic agents. The motor neurons are protected from many chemotherapy drugs by the blood brain barrier, and therefore the likely mechanism of chemotherapy associated foot drop is by axonal damage to the long peripheral motor neurons of the common perineal nerve.

Here we describe five cases of chemotherapy associated isolated peroneal nerve paresis resulting in foot drop after several cycles with platinum and/or taxanes. We postulate that chemotherapeutic agents contributed to peroneal nerve palsy in all the five cases. In all of these cases, no other plausible explanation was found for the foot drop. No clinically significant weight loss was reported in 4 out of the 5 cases and CNS disease was ruled out with imaging in 4 of the 5 cases. All patients who continued follow up showed complete recovery of motor function on discontinuation of offending agents and supportive treatment. To our knowledge, platinum and taxane induced isolated common peroneal neuropathy has not been widely reported.

Case Presentation

A 49 year old female with no past medical history presented with long standing hematochezia in April, 2017. On colonoscopy she was found to have a moderately differentiated rectal adenocarcinoma, Microsatellite Stable (MSS), KRAS mutated. Staging work up revealed a T3N0 tumor with no evidence of metastatic disease. She was started on neoadjuvant therapy with capecitabine 1000 mg/m^2 and concurrent radiation therapy for 5 weeks with no significant side effects. This was followed by low anterior resection with pathologic staging of the tumor: T3N1cM0. Adjuvant CAPOX (Capecitabine 1000 mg/m^2, Oxaliplatin 130 mg/m^2 every 21 Day cycle) was initiated. After 4 cycles, Oxaliplatin was discontinued due to progressive sensory neuropathy and debilitating grade 3 motor neuropathy of the peroneal nerves resulting in foot drop on the left. Motor strength of the left ankle dorsiflexion was 3/5 and rest of the motor exam was normal with 5/5 strength. MRI of the Lumbosacral spine did not show any acute findings. Over the next 4 months since discontinuing oxaliplatin, her left ankle dorsiflexion motor strength improved to 5/5.

An 85 year old male with a history of right sided colon cancer (T3N0M0) in 2010 treated with hemicolectomy and no adjuvant therapy presented with an elevated CEA of 205 ng/ml(Normal: 0.0 ng/ml to 3.0 ng/ml) in 2016. This prompted investigation with imaging which showed colon cancer recurrence in the liver. He underwent segment 5, 6 and 7 hepatic resection with pathology showing moderately differentiated adenocarcinoma of colonic origin, MSS, KRAS mutated. This was followed by adjuvant FOLFOX (Oxaliplatin 85 mg/m^2, Leucovorin 400 mg/m^2, Fluorouracil 400 mg/m^2, Fluorouracil 2400 mg/m^2). After completing 5 cycles of chemotherapy he was admitted to the hospital with acute onset diarrhea, weakness and an episode of syncope associated with left foot pain and weakness. On exam, he was found to have a left sided foot drop with a motor strength of 3/5 in the L ankle dorsiflexors. Patient then completed remaining chemotherapy without oxaliplatin and with 5-fluorouracil and leucovorin. Patient initiated physical therapy and wore a brace. Over the next 6 months his left sided foot drop resolved.

A 54 year old male presented in March, 2017 with early satiety which prompted an Esophagogastroduodenoscopy (EGD). He was found to have a mass in the lesser curvature of the stomach with pathology showing signet ring cell carcinoma of the stomach; MSS. Imaging showed metastatic disease with peritoneal carcinomatosis. He received palliative chemotherapy with FOLFOX for three months, and underwent repeat imaging with progression of disease. He was at this time switched to combination paclitaxel with ramucirumab. Patient received seven cycles of paclitaxel (80 mg/m^2, Day 1,8,15 of a 28 day cycle) when he was noted to have developed foot drop with a dorsiflexion motor strength of 3/5 bilaterally. Paclitaxel was discontinued and he underwent vigorous physical therapy with improvement in motor strength of the lower extremities over 4 months.

A 77 year old man renal dysfunction presented in April, 2016 with hemoptysis and dysphagia. An EGD revealed an obstructing mass in mid-esophagus 21 cm to 25 cm from incisors. He underwent endoscopic ultrasounds with esophageal stenting showing a T3N1 tumor with pathology consistent with poorly differentiated squamous cell carcinoma. PET/CT imaging showed hypermetabolic mediastinal nodes and hypermetabolic boney lesions in the thoracic spine, ribs and the scapula. He was started on single agent palliative paclitaxelat 80 mg/m^2 (Day 1,8,15 of a 28 day cycle). He tolerated it well and carboplatin was added on cycle 3, following which he developed acute onset bilateral foot drop with a 3/5 motor strength of the dorsiflexion. Imaging of the spine did not show any space occupying lesion. The condition was so debilitating that he could not walk and was admitted to the hospital followed by rehab where he began to regain dorsiflexion strength upon discontinuation of the chemotherapy. However, his overall performance status was declining. He eventually completed external beam radiation therapy to the esophageal mass and was transitioned to hospice per his wishes.

A 75 year old man presented in October, 2018 with new onset severe dyspepsia associated with weight loss. EGD showed an ulcer of the gastric antrum and pathology was consistent with moderately differentiated adenocarcinoma. Staging scans showed mass extending into the serosa with no evidence of lymph node involvement. He was started on perioperative FLOT (Docetaxel 50 mg/m^2, Oxaliplatin 85 mg/m^2, Fluorouracil 2600 mg/m^2 every 14 Day Cycle) which he tolerated well. After completing 4 cycles, patient underwent distal gastrectomy with Billroth II reconstruction with partial resection of left lobe of liver due to local extension. Pathologically the tumor was staged as a T4bN0 moderately differentiated adenocarcinoma, MSS, HER2 negative with positive liver margin. He completed 4 more cycles of FLOT followed by chemoradiotherapy with Capecitabine 1000 mg/m^2 in June 2018. Towards the end of his treatment, he was noted to have lost 25 lbs. of weight over 2 months. He developed L sided foot drop in June 2018 after completing treatment, with a motor strength of 3/5 associated with bilateral lower extremity numbness and tingling. His weakness showed gradual improvement with physical therapy over the next 2 months since discontinuing chemotherapy.

Discussion

The incidence of anti-cancer drug associated neurotoxicity remains unclear due to several confounding factors such as preexisting diabetes and nutritional deficiencies but estimated to be 52% to 68% [13,14]. Chemotherapy induced neurotoxicity tends to be dose dependent, cumulative and reversible though it may be persistent in a substantial proportion of patients. Taxanes and vinca alkaloids cause neurotoxicity by causing axonal damage (Axonopathy) to the large myelinated motor fibers whereas platinum accumulates in the dorsal root ganglion resulting in neuropathy. Motor nerves have the capacity for re-innervation of the muscle fibers, reflected clinically in the recovery of the patients' strength and function [15]. Although peroneal nerve palsy incidence is not well described for many of the neurotoxic chemotherapy agents, a large body of literature confirms increased risk of neurotoxicity with increasing exposure to the

Table 1: Summary of five patients presenting with foot drop secondary to treatment with platinum or taxane based chemotherapy.

Patient	Age/Sex	Diagnosis and Stage	Chemotherapy Regimen	No. of Cycles Before Onset	Cumulative Onset Dose	Treatment: Discontinuation Of Offending Agent Plus	Resolution
1	49/F	Rectal Adeno T3N1cM0	Neoadjuvant Capecitabine 1000 mg/m^2 +RT, Adjuvant Capecitabine 1000 mg/m^2 + Oxaliplatin 130 mg/m^2 every 21 Day cycle	4	Oxaliplatin 520 mg/m^2	Physical Therapy	4 months
2	85/M	Colon Adeno TxNxM1	mFOLFOX6 (Oxaliplatin 85 mg/m^2 + Leucovorin 400 mg/m^2 + Fluorouracil 400 mg/m^2 + Fluorouracil 2400 mg/m^2) every 14 Day cycle.	5	Oxaliplatin 425 mg/m^2	Physical Therapy	6 months
3	54/M	Gastric- Signet ring TxNxM1	FOLFOX for 6 cycles (Dose unknown) with POD, switched to Ramucirumab 8 mg/kg + Paclitaxel 80 mg/m^2 (Day 1,8,15 of 28 day cycle)	7	Paclitaxel 1680 mg/m^2	Physical Therapy	4 months
4	77/M	Esophageal SCC T3N1M1	Paclitaxel 80 mg/m^2 (Day 1,8,15 of 28 day cycle), Carboplatin AUC 6 added to cycle 3	3	Paclitaxel 560 mg/m^2	N/A	N/A
5	75/M	Gastric Adeno T4bN0M1	Perioperative FLOT (Docetaxel 50 mg/m^2 + Oxaliplatin 85 mg/m^2 + Fluorouracil 2600 mg/m^2 every 14 Day Cycle) followed by Capecitabine 1000 mg/m^2 +RT	8	Oxaliplatin 685 mg/m^2	Physical Therapy	2 months

Adeno: Adenocarcinoma; POD: Progression of Disease; RT: Radiation Therapy; SCC: Squamous Cell Carcinoma

neurotoxic drugs. Among the platinum compounds, Oxaliplatin is most commonly associated with neuropathy seen in 85% to 100% of the patients [16]. Cold induced dysesthesia is the characteristic complaint seen in these patients and it tends to resolve within a few weeks to up to 3 months of discontinuation of therapy or may become permanent [17-19]. The high incidence of CIPN in patients treated with Oxaliplatin is reflected in the results of the MOSAIC trial [20]. A total of 2246 patients who had undergone curative resection for stage II or III colon cancer were randomized to receive FL alone or in combination with oxaliplatin for six months. During treatment, 92% of patients on FOLFOX were noted to have neuropathy of any degree versus only 16% on the 5FU arm. At one month follow up, the prevalence of neuropathy in the FOLFOX group was down to 62% and further down to 41% at 6 months. At one year follow up, only 30% of these patients had persistent neuropathy. With increasing dose, this peripheral neuropathy can progress to more severe symptoms including continuous dysesthesia, burning, muscle cramping and jaw stiffness [21].

In 2017, the IDEA collaboration published a preplanned, pooled analysis of 6 clinical trials with over 12,800 patients, conducted concurrently to evaluate the non-inferiority of adjuvant therapy with either FOLFOX or CAPOX administered for 3 months, as compared with 6 months with the primary end point of DFS at 3 years. Though the study failed to meet its primary endpoint in its overall population, it did show that a shorter duration of adjuvant therapy was associated with significantly lower rates of neurotoxicity (16.6% with FOLFOX and 14.2% with CAPOX) than a longer duration (47.7% with FOLFOX and 44.9% with CAPOX), independent of the chemotherapy regimen. This study illustrates the cumulative nature of CIPN with oxaliplatin [22].

In contrast to oxaliplatin, another platinum compound cisplatin causes painful paresthesia or numbness in a stocking-glove distribution in 28% to 100% of patients [14,16]. These symptoms last up to 6 months or longer and may become permanent. In one retrospective study [23], 30% of patients continued to have worsening of symptoms after discontinuation of cisplatin. In another study [24], 20% of patients continued to have neuropathy 5 years after completing cisplatin based chemotherapy for testicular cancer. Carboplatin induced neuropathy is similar in presentation to cisplatin but usually milder. It is seen in 6% to 42% patients [16,25].

The taxanes also cause neuropathy clinically similar to cisplatin induced neuropathic symptoms. Paclitaxel is more neurotoxic and causes CIPN in 57% to 83% of patients, whereas docetaxel in 11% to 64% [25]. In 50% to 60% of patients, symptoms tend to resolve within 3 months with or without residual symptoms [26-28]. Nanoparticle albumin-bound paclitaxel (nab-PTX) is a commonly used taxane in the treatment of breast cancer. Several phases II/III randomized trials have reported a higher incidence of CIPN on nab-PTX compared to paclitaxel and docetaxel with an estimated incidence of 75% [29]. CIPN associated with nab-PTX usually resolved rapidly within 3 weeks to a month. Cabazitaxel, a relatively newer taxane used in the treatment of hormone refractory prostate cancer has been shows to be less neurotoxic compared to docetaxel with an incidence of 11% to 12% [30]. Other agents known to cause neuropathy include vinca alkaloids, Bortezomib, IMIDs and Ixabepilone.

Several cases of foot drop have been reported in the pediatric population after treatment with vincristine for acute lymphoblastic leukemia [2] with an estimated incidence of 5% to 10% [31]. A single case of capecitabine associated foot drop has also been described [32]. To our knowledge foot drop as a manifestation of peripheral neuropathy has been under reported in patients treated with platinum and taxane compounds.

Among the five patients presented in this series, patients 3.4 and 3.5 (Table 1) were treated with both a platinum and a taxane and it is therefore difficult to implicate one agent as the cause of foot drop. Literature suggests a cumulative dose of 100 mg/m^2 to 300 mg/m^2 of paclitaxel and 75 mg/m^2 to 100 mg/m^2 of docetaxel prior to onset of CIPN, whereas Oxaliplatin can cause CIPN at any dose, though

it tends to be more persistent at a cumulative dose of 750 mg/m^2 to 800 mg/m^2. The cumulative onset dose for cisplatin is 300 mg/m^2 and 800 mg/m^2 to 1600 mg/m^2 for carboplatin [25]. In the five patients presented (Table 1), the cumulative dose prior to developing foot drop was: Oxaliplatin 425 mg/m^2 to 685 mg/m^2, Paclitaxel 560 mg/m^2 to 1680 mg/m^2, Carboplatin 335 mg/m^2 and Docetaxel 400 mg/m^2. Time to resolution of symptoms after discontinuation of neurotoxic chemotherapy ranged from 2 months to 6 months (Table 1). Four of the five patients had CNS imaging to rule out other causes of peroneal nerve palsy. As clinicians become more aware of foot drop as a complication of neurotoxic chemotherapy and with the absence of other symptoms, perhaps there will be less need to perform expensive imaging tests in the work up of this chemotherapy adverse effect.

Treatments of chemotherapy induced foot drop include decreasing dose and frequency of offending agent and at times, discontinuation may be necessary. The phase 3 MRC COIN trials [33] compared intermittent versus continuous oxaliplatin and 5FU combination chemotherapy for first-line treatment of metastatic colorectal cancer. Though it failed to show non-inferiority, it did show that grade 3 or worse peripheral neuropathy was more frequent on continuous than on intermittent treatment (27% *vs.* 5%). An ankle-foot orthosis splint stabilizes the ankle in stance and helps clear toes in the swing, therefore preventing injury on ambulation and should be used until active movement has recovered [34]. As described in the cases above, patients tend to recover full motor function on discontinuation of causative chemotherapeutic agent. Physical rehabilitation under the supervision of a physical therapist to include passive and active range of motion and muscle strengthening is also recommended to hasten recovery [25,35].

No study has specifically looked at pharmacotherapy for the treatment of motor neurotoxicity. In patients with associated sensory symptoms, a trial of duloxetine may be a reasonable option. Duloxetine has been shown in a randomized, double-blind, placebo-controlled crossover trial of 231 patients to result in a greater reduction in pain compared to placebo among patients with painful chemotherapy-induced peripheral neuropathy with a modest benefit [36]. Two studies demonstrated safety and modest efficacy of venlafaxine for the management of CIPN secondary to taxanes and platinum [37,38]. Other agents with mild-moderate activity for chemotherapy induced neuropathy symptoms include gabapentin, pregabalin, nortriptyline, desipramine [39]. It is unclear if these agents will expedite the recovery of peroneal nerve palsy. None of these agents were used to treat the five patients in this series. In our opinion, pharmacotherapy should be reserved for patients in whom foot drop does not improve with supportive measures.

Currently there are no established therapies to prevent development of chemotherapy induced neuropathy. A total of 42 randomized controlled trials have evaluated the efficacy of various pharmacological agents in the prevention of CIPN. These studies included anticonvulsants, antidepressants, vitamins, minerals, and other chemoprotectants. None of these agents are currently recommended for prevention of CIPN due to the paucity of high quality evidence [40]. The only successful strategy to date has been to decrease the cumulative dose and duration of the offending chemotherapy as was seen on the IDEA trial [22] whenever oncologically indicated.

Conclusion

Foot drop is an underreported complication of taxane and platinum based chemotherapy. The motor neurons are protected by the blood brain barrier, and therefore the likely mechanism of foot drop is by axonal damage to the long peripheral motor neurons of the common perineal nerve. Treatment of foot drop includes discontinuation of the offending agent, ankle orthosis/brace to provide foot support as well as physical therapy. No effective strategies have been shown to prevent development of CIPN. Duloxetine or venlafaxine may be used in patients with associated neuropathic pain symptoms, though their efficacy in treating motor neuropathy remains to be evaluated in further studies. Clinicians should be aware of foot drop as a potential neurotoxic complication of platinum and taxane classes of chemotherapeutic agents. Further studies to prevent the development of chemotherapy induced neurotoxicity are warranted.

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