Anti-Cancer Drugs, **3**, pp. 375–377

Case report

Cisplatin-related Lhermitte's sign

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The sensation of a sudden electrical impulse travelling along the spine to the legs and feet on flexion of the neck has been known as Lhermitte's sign. Lhermitte's sign, as part of cisplatin-related neurotoxicity, was observed in four patients, with ovarian or lung cancer, simultaneously with peripheral neuropathy, after a dose of 375–700 mg/m^2. The dose intensity (DI) of cisplatin in our patients ranged from 12.5 to 26.9 mg/m^2/week. No direct relationship was found between DI and the timing of Lhermitte's sign. Other relevant causes for this sign were ruled out. The mechanism responsible for the development of Lhermitte's sign is unclear. Interruption of treatment with cisplatin may not prevent the appearance of Lhermitte's sign. In most of the reported cases in the literature this sign developed after the end of cisplatin courses.

Key words: Cisplatin, Lhermitte's sign, neurotoxicity.

Introduction

The sensation of a sudden electrical impulse travelling along the spine to the legs and feet on flexion of the neck has been known as Lhermitte's sign. It has been described in relation to multiple sclerosis, cervical spondylosis, cervical spinal cord tumors, radiation myelopathy and head injuries, B12 deficiency, and cisplatin toxicity.[1] We present four cancer patients who were treated with cisplatin-containing regimens and developed Lhermitte's sign.

Case reports

Patient no. 1

A 43 year old woman underwent a right modified radical mastectomy for a stage I infiltrating ductal carcinoma and irradiation of the chest wall in 1980. Breast reconstruction was performed a year later. She was disease-free till December 1990, when she complained of abdominal pain. Following a diagnosis of an ovarian mass, she underwent an explorative laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy, leaving only small residual disease. A serous papillary adenocarcinoma of the ovary, stage IIIc, was an indication for chemotherapy. Six 3 week courses of cisplatin (75 mg/m^2) and cyclophosphamide (CP; 750 mg/m^2) were administered, combined with metoclopramide, dexamethasone and ondasetron as anti-emetics, to April 1991, yielding a partial response. Cisplatin-related toxicity was severe, and included nausea, vomiting, fainting, anemia, thrombocytopenia and lethargy. Three more CP courses were to be given, but after the seventh course the patient complained of lethargy and a sensation of electrical impulses in her upper and lower limbs on flexion of the neck. No other neurological symptoms or signs were found. Serum electrolytes, including calcium and magnesium, were within the normal range. Cisplatin was ommitted from the treatment. The symptoms improved after 6 months. The total dose of cisplatin given was 525 mg/m^2 with a dose intensity (DI) of 21.8 mg/m^2/week.

Patient no. 2

A 60 year old woman who had a 6 year history of a right modified radical mastectomy for a T2N1MO infiltrating ductal carcinoma of the breast received adjuvant chemotherapy with CP (500 mg/m^2), methotrexate (40 mg/m^2), 5-fluorouracil (600 mg m^2), vinblastine (5 mg m^2) and adriamycin (50 mg m^2),

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and remained disease-free. In January 1991 she complained of abdominal distention and pain. An abdominal ultrasound scan demonstrated bilateral ovarian masses. A stage IIIc serous papillary cystadenocarcinoma of the ovary was found on an explorative laparotomy. Bilateral salpingo-oophorectomy and omentectomy were performed, leaving a large residual disease in the abdominal cavity. Five courses of CP resulted in a minimal response of short duration. Cisplatin-related toxicity included nausea, vomiting, allopecia, anemia, leukopenia and fever necessitating admition and parenteral antibiotic treatment, weakness of the arms, and numbness and paraesthesias in the fingers. One month following interruption of CP she complained of a sensation of electrical impulses along the feet and legs while flexing the neck. No other pathology was found on physical examination. Serum electrolytes were within the normal range at the time of the appearance of Lhermitte's sign. The symptoms improved after 4 months, but the peripheral neuropathy, thus far, still exists. The total dose of cisplatin given was 375 mg/m^2 with a DI of 17.8 mg/m^2/week.

Patient no. 3

A 62 year old male with a history of ischemic heart disease, myocardial infarction and congestive heart failure underwent a chest pain radiograph for an intercurrent upper respiratory infection in December 1990. Left pleural effusion and a left upper lobe mass were found, proven cytologically to be a small cell carcinoma of the lung. Systemic evaluation demonstrated liver metastases on an abdominal computed tomography scan and increased uptake on a ^{99}Tc bone scan, histologically proven as metastases. Six 3 week courses of etoposide (100 mg/m^2/day) on days 1, 3, 5, and cisplatin (20 mg/m^2/day) on days 1–5 were administered, resulting in a complete response in the liver and in the chest, but in only stabilization in the bones. Cisplatin-related toxicity included severe paraesthesias in both legs and hands. Cisplatin was replaced by carboplatin (300 mg/m^2) in May 1991, and 1 month later the patient complained of a sensation of electrical impulses along the hands and legs while flexing the neck and the upper back. No other neurological signs were found. Serum electrolytes were within the normal range. Chemotherapy was interrupted because of toxicity, lack of cancer-related symptoms and incurable disease at this stage. The patient expired after 2 months due to brain involvement. The total dose of cisplatin given was 700 mg/m^2 with a DI of 26.9 mg/m^2/week.

Patient no. 4

A 54 year old female underwent total abdominal hysterectomy, bilateral salpingo-oophporectomy and omentectomy for a stage IIIc G2 serous papillary adenocarcinoma of the ovary in January 1991. The postoperative CA-125 level was 3850 U/ml. Six courses of CP chemotherapy were administered within 20 weeks, combined with metoclopramide and dexamethasone, rendering the patient disease-free. Three months following the last course of CP the patient complained of lethargy, numbness of the fingers and toes in both the hands and feet ('socks and gloves'), a sensation of electrical impulses along the hands and legs while flexing the neck when sitting and progressive inability to perform fine daily activities with her fingers, e.g. holding a pen. Neurological examination demonstrated preserved fine touch and pick sensation, preserved proprioception and muscular strength, impaired deep sensation and vibration distal to the knees, and lack of Achilles and patellar tendon reflexes. Radiological examination of the spine was normal. Serum levels of folic acid, vitamin B12, calcium and magnesium were normal. No treatment was recommended and full recovery of the neurologic picture occurred 4 months later with no evidence of disease relapse. The total dose of cisplatin given was 450 mg/m^2 with a DI of 12.5 mg/m^2/week.

Discussion

Lhermitte's sign in cisplatin-treated patients has only been rarely reported over the past decades. However, with the increasing use of cisplatin for a wide range of malignancies, this sign is now more frequently observed. The development of Lhermitte's sign in a previously unirradiated, but chemotherapy-treated cancer patient should raise the possibility of cisplatin neurotoxicity, as well as other causes such as B12 deficiency, cervical spondylosis and metastatic spread to the meninges.[1]

Lhermitte's sign was observed in four patients. Since cisplatin was the only common drug to all of them, neurotoxicity was related to this drug. Other relevant causes for this sign were ruled out. Patient 1 was irradiated to the chest wall because of a breast cancer. The cervical spinal cord was not included

in the irradiated field. Vitamin B12 levels were normal in all patients. Cervical spondylosis was present in two patients, most probably prior to the administration of cisplatin. None of the patients in our series had a meningeal spread nor signs of a cervical myelopathy. The fact that there was no worsening of symptoms and neurological findings in three of our patients after interruption of cisplatin treatment, while the disease was gradually progressing, suggests that Lhermitte's sign was treatment related and not disease related.

Two of our patients, as one reported case,[2] had two metachronous primary cancers, of which the second cancer was treated by cisplatin chemotherapy. The relation between the two primary cancers and the probability of developing Lhermitte's sign is not known. According to the literature, it seems that there is no relation between the type of the primary cancer and the development of this sign.[2,5]

Lhermitte's sign accompanied peripheral neuropathy in our series and in most of the reported cases in the literature.[2,5] Some authors, however, claimed that Lhermitte's sign preceded the polyneuropathy by a couple of months.[3]

Early signs of cisplatin-related peripheral neuropathy, according to literature data, included decreased vibratory sensibility in toes after a mean dose of 417 $\pm$ 132 mg/m^2 and loss of ankle jerks after a mean dose of 455 $\pm$ 86 mg/m^2. Paraesthesias appeared after a higher dose. Strength was unaffected. Sural nerve response abruptly disappeared in six out of 11 patients after 383 $\pm$ 103 mg/m^2.[6] All of our patients were treated with high dose cisplatin, yielding a cumulative dose range of 375–700 mg/m^2. The time interval between the first administration of cisplatin and the appearance of neuropathy corresponded, in one report, to three courses of chemotherapy.[7] In our series six or seven courses were needed to cause Lhermitte's sign, as also reported by Walther *et al.*[1] The wide range of cisplatin doses needed to evoke Lhermitte's sign indicates that this phenomenon is not dose dependent.[5] The DI of cisplatin in our patients ranged from 12.5 to 26.9 mg/m^2/week. No direct relationship was found between the dose intensity and the timing of Lhermitte's sign, although in the case with the lower DI the sign developed relatively later than in the other cases. Since the DI was not calculated in other series, it is impossible to determine its role in the development of Lhermitte's sign.

The mechanism responsible for the development of Lhermitte's sign is unclear. In multiple sclerosis and in subacute degeneration of the spinal cord central demyelination might be the basic pathology. It is suggested in the literature that central demyelination should be suspected in cisplatin-related Lhermitte's sign,[1,4] because scattered destruction of myelin sheaths was found in patients with cisplatin-induced peripheral neuropathy.[7] Electron microscopy of peripheral nerves from four patients showed axonal degeneration and secondary myelin breakdown. Cisplatin concentrations in the tumor, sural nerve and spinal ganglia were similar, but in the brain they were lower. This may explain the relative sparing of the brain from cisplatin toxicity.[6]

Interruption of cisplatin treatment may not prevent the appearance of Lhermitte's sign. In most of the reported cases in the literature this sign developed after the end of cisplatin courses.[4] The duration of Lhermitte's sign varied from 1 to 8 months.[5] Recovery is slow. Exacerbation of Lhermitte's sign and symptoms of peripheral neuropathy were reported in a young adult following a 100 yard run, a long time after being in a complete remission.[8]

To conclude, Lhermitte's sign may be a part of cisplatin-related neurotoxicity. Its development is not dose dependent, but rarely occurs below 350 mg/m^2. The relation of this sign to the DI of cisplatin is not yet clear.

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(Received 12 June 1992; accepted 17 June 1992)