

## 5-Fluorouracil induced late peripheral neuropathy. Case report

### *Neuropatia periférica tardia induzida pelo 5-Fluorouracil. Relato de caso*

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#### ABSTRACT

**BACKGROUND AND OBJECTIVES:** Peripheral neuropathy caused by chemotherapeutic drugs is today one of the major limiting factors in cancer pharmacological therapy due to its negative influence in the cancer patient's quality of life. Its incidence varies depending on the pharmacological nature of the therapy used. Peripheral neurotoxicity caused by 5-Fluorouracil was scarcely described, being characterized as rare adverse effect of this drug. The objective of this study is to report a 5-Fluorouracil induced late peripheral neuropathy case treated at the Pain Clinic, with standard care for neuropathic pain.

**CASE REPORT:** Female patient, 62 years old, undergoing 5-Fluorouracil chemotherapy 2520mg/week in 5 cycles of 360mg/day continuous infusion to treat colorectal cancer. Three months after the end of the cycle she reported burning pain and hand and foot dysesthesia with proximal irradiation and allodynia. She was referred to the Pain Clinic 2 years after the symptoms onset. The treatment started with gabapentin and she was advised to have psychiatric follow-up and physical exercises. The Visual Numeric Scale was used to assess pain. In less than 6 months the patient reported pain improvement with values reduced from 10 to 2.

**CONCLUSION:** Although uncommon, peripheral neuropathy can occur as permanent toxicity due to 5-Fluorouracil chemotherapy and should be early identified and treated to improve patient's quality of life.

**Keywords:** Anticonvulsant, Chemotherapy, Chronic pain, Fluorouracil, Gabapentin, Neurotoxicity.

#### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** A neuropatia periférica causada por quimioterápicos é hoje um dos principais fatores limitantes do tratamento farmacológico do câncer, devido a sua influência negativa na qualidade de vida do paciente oncológico. Sua incidência varia com a natureza farmacológica da terapia utilizada. A neurotoxicidade periférica causada pelo 5-Fluorouracil foi pouco descrita, sendo caracterizada como efeito adverso raro deste quimioterápico. O objetivo deste estudo foi relatar um caso de neuropatia periférica tardia induzida por 5-Fluorouracil atendido na Clínica de Dor com tratamento padrão para dor neuropática.

**RELATO DO CASO:** Paciente do sexo feminino, 62 anos, submetida a quimioterapia com 5-Fluorouracil protocolo 2520mg/semana em 5 ciclos de infusão contínua de 360mg/dia para tratamento de câncer colorretal. Três meses após o fim do ciclo apresentou dor em queimação e disestesia em mãos e pés, com irradiação proximal e alodínea. Foi encaminhada à clínica de dor 2 anos após o começo dos sintomas. Iniciou-se o tratamento com gabapentina e foi orientada a fazer acompanhamento psiquiátrico e realizar exercícios físicos. Para a avaliação da dor foi utilizada a escala visual numérica. Em menos de 6 meses a paciente referiu melhora da dor com redução de valores de 10 para 2.

**CONCLUSÃO:** Apesar de incomum, a neuropatia periférica pode ocorrer como toxicidade permanente da quimioterapia com 5-Fluorouracil e deve ser precocemente identificada e tratada para proporcionar melhora da qualidade de vida do paciente.

**Descritores:** Anticonvulsivante, Dor crônica, Fluorouracil, Gabapentina, Neurotoxicidade, Quimioterapia.

#### INTRODUCTION

Peripheral neurotoxicity from the chemotherapy in cancer treatment is relatively common, and this effect can be considered one of the major limiting factors in the use of some chemotherapeutic drugs. Neuropathy deeply affects daily life, handling objects, eating, working, with personal hygiene and it is also associated with a great psychological distress<sup>1</sup>.

The fluoropyrimidine antimetabolite 5-Fluorouracil (5-FU) started to be clinically used as an anticancer agent 40 years ago. Today it is commonly used as a chemotherapy component for a wide range of epithelial neoplasias<sup>2</sup>. Its toxicity spectrum differs according to the management protocol, and the most common adverse effects are stomatitis, diarrhea, myelosuppression and skin toxicity. Neurotoxicity is far less common (incidence of 2 to 5%)<sup>3</sup>. The generally described syndrome is central, with an acute brain disorder, characterized by ataxia, which can be

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accompanied by muscle weakness, bilateral paralysis of the oculomotor nerve and signs of involvement of the first motor neuron. These symptoms are usually reversible with the discontinuation of the drug<sup>2</sup>.

Peripheral neurotoxicity is common after the administration of 5-FU in combination with agents that are notably known as producers of cumulative peripheral neuropathy, the platinum-based agents (e.g.: oxaliplatin). In colorectal cancer, protocols that use 5-FU/LV (leucovorin) plus oxaliplatin are currently considered standard for first-line therapy both adjuvant and palliative<sup>4</sup>.

Up to now, the cases of induced peripheral neuropathies associated with 5-FU as single therapy have seldom been described<sup>5</sup>. The objective of this study was to report a case of late and persistent peripheral neuropathy after 5-FU chemotherapy.

## CASE REPORT

Female patient, 62 years old, with a history of colorectal cancer diagnosed 4 years ago. Her major complaint was burning pain in the upper and lower limbs (LL and UL). The cancer treatment was radiation therapy associated with 5-FU chemotherapy - protocol 2520 mg/week in 5 cycles of continuous infusion of 360mg/day - successful. Three months after finishing chemotherapy, she complained of intense and continuous burning pain, in the hands and feet, associated with paresthesia and allodynia. These symptoms worsened with emotional stress.

She was referred by the oncology service to the pain clinic two years after the beginning of the painful symptoms. She was very grieved and depressed. During the physical examination, she reported burning pain in the arms and legs, extending up to the shoulders and pelvis. Normal gait, strength and superficial and deep reflexes preserved in LL and UL. No signs of meningeal irritation. Paresthesia in the fingertips and allodynia regions extending to the four limbs. DN4 5 in 10 (burning, tingling, pricking and pain when brushing). The intensity of pain assessed by the visual numeric scale (VNS) was 10, maximum score. No myofascial tender points. Lumbosacral nuclear magnetic resonance (NMRI) showed evidence of small disc protrusion in L<sub>4</sub>-L<sub>5</sub> and L<sub>5</sub>-S<sub>1</sub> with no significant alterations.

Although not frequent, after 5-FU single therapy, we thought about the possibility of the diagnosis of chemotherapy-induced late neuropathy. Other causes of peripheral neuropathy were discarded, such as diabetes mellitus, vitamin B<sub>12</sub> deficiency, autoimmune diseases, infections, and traumas.

We started the treatment with gabapentin (300mg every 8 hours, a total of 900mg/day), as well as advice to practice regular physical activities.

In the second visit, with a 2-month interval, the patient reported irregular walking practice and regular use of gabapentin, reporting 50% improvement in pain (VNS=5). She was anxious, complaining of mood fluctuations. She was referred to Psychiatry and the night dose of gabapentin was increased to 600mg (total 1200mg/day).

In the third visit, also with a 2-month interval, the patient was in good spirits, with regular use of gabapentin (300-300-600mg

associated to fluoxetine (20mg/day) and alprazolam at night (2mg). Practicing regular water aerobics exercises and walking. In the physical exam, she presented paresthesia in hands and feet without irradiation and without allodynia (VNS=2).

The patient is in follow-up at the pain clinic, with periods of improvement and worsening of the symptoms and the emotional state. She is taking gabapentin and in psychiatric follow-up.

## DISCUSSION

Peripheral neuropathy is commonly reported as a frequent complication of the 5-FU systemic combination therapy with similar platinum-based agents, showing the incidence of up to 90%<sup>1</sup>. However, the incidence and severity of neurotoxicity appear to be associated with the single platinum-based drug, that is, the peripheral neuropathic involvement would occur regardless of the use of 5-FU as adjuvant<sup>2</sup>.

Moreover, the vast majority of the reported cases of neurotoxicity caused by 5-FU alone are central and reversible neuropathic conditions after treatment discontinuation<sup>6</sup>.

In this case, probably due to these reasons, the diagnosis of persistent late peripheral neuropathy associated with 5-FU chemotherapy was long neglected, which aggravated the condition.

However, through documented bibliographic review and after ruling out other causes of peripheral neuropathy, we thought about the possibility of the case in question be a rare secondary condition to the chemotherapy used.

Argyriou et al.<sup>7</sup> carried out a clinical trial with 150 patients treated with the Folfox (oxaliplatin + 5-FU) or Xelox (oxaliplatin + capecitabine) protocols, followed during 18 months and comparatively evaluated for the onset of the neurotoxicity symptoms. No significant difference was observed in the incidence of acute neurotoxicity (84.4% in the Folfox group and 79.5% in the Xelox group). However, the Folfox protocol showed an increased incidence of chronic neurotoxicity compared with the Xelox (83.1% vs. 60.3%). In addition to higher incidence, patients treated with Folfox showed more intense chronic peripheral neuropathy.

These findings suggest the 5-FU participation in the development of peripheral neurotoxicity induced by combination chemotherapy<sup>7</sup>.

In the case reported, it was observed the presence of chronic neurotoxicity with the use of 5-FU alone.

Stein et al.<sup>3</sup> reported two cases of patients who have developed peripheral neuropathy associated with the 5-FU therapy. Both patients underwent postoperative radiation and 5-FU in intravenous bolus on the first day and in the last 3 days of radiation. Six weeks after receiving the adjuvant chemotherapy with 5-FU + levamisole 3 doses per day for 5 consecutive days per month.

During the chemotherapy, the first patient developed pain in the legs with dorsiflexion weakness and reduction of tactile and vibratory sensitivity. Neurophysiological studies were consistent with demyelinating polyneuropathy diagnosis involving mainly the large fibers. The adjuvant therapy was discontinued, with symptoms stabilization. After 3 months, this patient had liver metastases, and the 5-FU/LV chemotherapy was reintroduced

for 5 consecutive days. In the first infusion, the patient already presented symptomatic neurological deterioration, confirmed by physical examination and neurophysiological study, being necessary to discontinue the treatment<sup>3</sup>.

The second patient complained of pain and weakness in the LL after 6 months of 5-FU/LV monthly cycles. The neurological examination showed the absence of distal alterations in deep tendon reflexes, but with reduced tactile and vibration sensitivity and ataxia. Neurophysiological studies showed demyelinating polyneuropathy of large fibers<sup>3</sup>.

Werbrouck, Pauwels and De Bleecke<sup>5</sup> reported a case of peripheral neuropathy associated with the 5-FU chemotherapy. That patient developed late syndrome after finishing the last drug cycle. The characteristics of the neuropathy reported by Stein et al.<sup>3</sup> and Werbrouck, Pauwels and De Bleecker<sup>5</sup> are similar to the ones of the present study. It is worth mentioning that, corroborating our results, the symptoms were also irreversible, even after treatment discontinuation. This suggests a possible subclinical lesion of nerve fibers during chemotherapy.

Oxaliplatin-induced chronic neurotoxicity is well-documented and demonstrated in several studies in the literature<sup>7</sup>. Its prophylaxis and treatment are being studied in promising pharmacological schemes that have already been described. The patient in this study presented a satisfactory response to gabapentin, which is also used in the treatment of oxaliplatin-induced neuropathy, as described by Grothey<sup>4</sup>. This association allows for a comparison between the pathophysiologies

responsible for each of the clinical contexts and the use of similar therapeutic schemes.

## CONCLUSION

Although the neurotoxicity of 5-FU is classically associated with the central nervous system involvement, the professionals involved in cancer patients care should be attentive to a possible relation between 5-FU and a peripheral demyelinating disease.

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