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PERIPHERAL NEUROPATHY INDUCED BY EXEMESTANE: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Introduction: Breast cancer represents the second leading cause of death among women from cancer in the world. Within this context, the use of adjuvant endocrine therapy is recommended to prevent the recurrence of this injury. Although aromatase inhibitors significantly decrease the recurrence of this neoplasia in women after menopause, such drugs can be associated with important adverse effects. The aim of this article is to report, possibly, the first case of peripheral neuropathy induced by the use of exemestane, and to perform a bibliographic review on the main evidence available in the literature on chemotherapy-induced peripheral neuropathy. **Case Report:** HFA, 84 years old, female, with a history of breast cancer and mastectomy, 3 and 2 years ago, respectively, using exemestane, complaining of paresthesia in the palms and plants. After the interruption of the exemestane treatment, there was a partial, but notable, improvement in the condition. **Discussion:** We believe in a possible causal relation given previous reports of neuropathy caused by drugs with an endocrine effect in anticancer therapy, in addition to the significant improvement after the suspension of exemestane. **Conclusion:** Large clinical studies are mandatory to confirm the possible causal relationship between exemestane and peripheral neuropathies.

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INTRODUÇÃO

Cancer is conceptualized as a multicausal pathology and classified as a chronic-degenerative disease that affects thousands of people each year[1]. In women, breast cancer is the most common malignancy, especially in individuals over 50 years[2]. According to the National Cancer Institute, this injury is the second largest responsible for deaths from cancer in women[2]. Within this context, different scientific studies, since 1986, address the estrogenic action in breast tumors that have hormonal receptors[2]. Thus, antineoplastic therapies were created to block such an effect. The first-line hormonal therapy, so far, is done through selective estrogen receptor modulators, especially tamoxifen. Although this drug represents good results, it is common for patients to become resistant to its effect throughout treatment[2].

Thus, other drugs have been developed to prevent the recurrence of this tumor, with emphasis on third generation aromatase inhibitors[3,4]. Aromatase is an enzyme responsible for the peripheral conversion of androgen to estrogen, which is the major source of estrogenic production in menopausal patients[5]. Although the use of aromatase inhibitors significantly reduces the recurrence of breast cancer in women after menopause, such drugs can be associated with important adverse effects, such as: reduction in bone mineral density, manifestations of menopause and musculoskeletal symptoms (polyarthralgia, morning stiffness, tenosynovitis, trigger finger and carpal tunnel syndrome)[6,7,8]. In addition to these events, a report was found pointing to a possible causal relation between the use of such a class of drugs and the development of peripheral neuropathy[9]. The symptoms resulting from neuropathy compromise the patient's daily activities by making it difficult to handle goals, food, work, and personal hygiene[10]. In addition, peripheral neuropathy is often

associated with great psychological distress[10]. When associated with strong intensity, neuropathy resulting from antineoplastic treatment may be responsible for the early interruption of treatment, which was observed in about a quarter of patients using aromatase inhibitors[11,12]. Early interruption of antineoplastic therapy is associated with increased mortality[13]. In view of the above, it is evident that peripheral neuropathy is a serious and significant adverse effect. Thus, this article aims to report what we believe to be the first case of peripheral neuropathy induced by the use of exemestane, and through this proposing a bibliographic review about the main evidence available in the literature on chemotherapy-induced neuropathy.

CASE REPORT

HFA, 84 years old, female, retired and with previous illnesses (glucose intolerance and hypercholesterolemia) undergoing treatment. History of breast cancer 3 years ago, with subsequent total mastectomy on the right 2 years ago. She denies neoadjuvant therapies. In use of adjuvant chemotherapy with exemestane for 1 year and 9 months. She reports onset of symmetrical polyarthralgia since March 2020, associated with myalgia and paresthesias in palms and plants. She had been diagnosed with fibromyalgia, and started treatment with duloxetine and gabapentin, however without improvement. On examination, she has deep reflexes abolished, tactile, thermal and dolorous hypoesthesia in the distal, brachial and crural thirds, besides distal hypopesthesia, muscle strength is preserved. Laboratory tests showing fasting glycemia of 117 mg / dL, Hb1ac 5.8%, C-Reactive Protein 3.8mg / dL, reagent FAN, reagent metaphasic plate with dense fine dotted pattern. Electroneuromyography showing a suggestive picture of sensory-motor polyneuropathy with axonal and distal predominance, affecting the four limbs, with predominance in the lower limbs. After the consultation, exemestane had been suspended with a partial improvement of the condition. At the clinical reassessment, carried out after 3 months, the patient reports a mild painful joint condition and a feeling of paresthesia, although there is still impairment of superficial and deep sensitivity in addition to abolished tendon reflexes.

DISCUSSION

Here we present the case of a patient with Peripheral Neuropathy after 1 year and 9 months of treatment with exemestane. We believe in a possible causal relation in view of previous reports of neuropathies resulting from the use of other drugs with an endocrine effect in anticancer therapy[9], in addition to the significant improvement after its suspension. Even so, since there is no evidence regarding the association, the development of peripheral neuropathy after aromatase inhibitor therapy may indicate only a coincidence, without any causal relation. Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse event that affects 38% of patients receiving treatment with multiple agents[14]. Aromatase inhibitors have been reported to have a possible causal relation with this syndrome[9]. Such a possibility had been considered as an adverse effect of chemotherapy, development of autoimmunity as part of the paraneoplastic process if there was a recurrence of malignancy, or neuropathy due to cryoglobulinemia-related vasculitis[9]. On the other hand, in a German cohort in which a significant prevalence of peripheral neuropathy was evidenced as a long-term sequel to adjuvant drug therapy for breast cancer, mainly related to the use of taxanes, aromatase inhibitors were reported only related to polyarthralgia and changes in libido[15]. In general, the pathophysiology of CIPN is described as bilateral symmetric axoniopathy, which results from the involvement of the dorsal root ganglia[16,17]. The dorsal root ganglion is more vulnerable to neurotoxicity since it is less protected by the nerve-hematological barrier, which explains the sensitive predominance of this type of neuropathy[18,19] even within the pathophysiological mechanisms of CIPN, today the role of neuroimmune interaction, given that the release of cytokines and chemokines are capable of triggering peripheral neural injury[16]. Within this context, it is worth noting that a pathogenic link between aromatase inhibitors and autoimmune reactions is hypothesized[20-23]. The development and severity of CIPN are directly associated with the type of drug, its dosage, the number of treatment cycles performed, previous or concomitant administration of neurotoxic antineoplastic agents and the type of compromised nerve fiber[24,25]. The presence of previous comorbidities associated with the appearance of peripheral neuropathies, such as diabetes mellitus, as well as alcoholism, are factors that often predispose the appearance and intensity of CIPN, even at low doses of antineoplastic agents[25].

The CIPN can manifest itself with motor, sensory or autonomic symptoms, with sensitive ones being frequently more relevant[16]. Motor symptoms are manifested as distal paresis, disturbances in gait, changes in balance, and disturbances in fine motor coordination[16]. Among the autonomic symptoms, one can mention the oscillation of systemic blood pressure, intestinal constipation, erectile dysfunction and urinary retention [16,26]. On the other hand, sensory symptoms consist of symmetrical paresthesia (the report of "feeling of wearing socks or gloves" is frequent). In addition, neuropathic pain may be present[16]. Neuropathic pain is defined as pain caused by disease or injury to the somatosensory system[27]. It is often described as "burning" pain and "shock sensation" involving hands and feet[16,27]. Neuropathic pain has an estimated incidence of 40% of patients with pain in cancer. Patients with CIPN, however, are three times more likely to develop neuropathic pain after the thermal treatment[27]. Patients who develop neuropathic pain appear twice as often at health services, need more care and more pharmacological treatment than patients with non-painful CIPN.[16,27] The National Cancer Institute (INCA) classifies peripheral neuropathy in different degrees, so that: grade I corresponds to reduced reflexes and mild paresthesia, grade II corresponds to hypoesthesia and intermediate paresthesia, grade III to intense decrease in sensitivity and, finally, grade IV corresponds to the lack of reflexes and sensitivity[28].

The CIPN is often associated with mood disorders, such as depression, anxiety or sleep disorders, which are of proportional severity to the intensity of CIPN[29]. In addition, reports of cognitive impairment, non-adherence to treatment and loss of self-care capacity were found. Difficulties in driving, tactile and thermal dysesthesia, difficulty walking in heels, buttoning blouses, combing hair or even cooking were reported by patients with breast cancer and CIPN[29]. It is a fact that third generation aromatase inhibitors represent a major advance in the treatment of breast cancer in postmenopausal women, and that this expands the options of endocrine breast cancer therapy, especially in patients who develop resistance to the effect of tamoxifen. Although the neurological adverse events associated with such medications are rare, they can occur. Thus, clinical trials aimed at investigating the development of symptoms of peripheral neuropathy in patients using exemestane are necessary, given that such injury significantly compromises the quality of life of patients.

Conclusion

Drugs that inhibit the aromatase enzyme represent an important tool in breast cancer treatment. Our case report and literature review highlight that therapy with aromatase inhibitors for breast cancer can trigger the appearance of peripheral neurological changes. However, the pathogenic mechanism behind the development of CIPN, after treatment with aromatase inhibitors, still remains unexplored. Therefore, preclinical studies are essential to investigate the pathophysiology through which the use of exemestane can induce peripheral neuropathies, just as large clinical studies are mandatory to confirm the possible causal relation between exemestane and peripheral neuropathies.

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