Neutropenic Enterocolitis in a Breast Cancer Patient using Adjuvant Chemotherapy: Case Report

Enterocolite Neutropênica em Paciente com Câncer de Mama em Uso de Quimioterapia Adjuvante: Relato de Caso

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Enterocolite Neutropênica em Paciente com Câncer de Mama em Uso de Quimioterapia Adjuvante: Relato de Caso

Enterocolitis Neutropénica en Paciente con Cáncer de Mama que Usa Quimioterapia Adyuvante: Reporte de Caso

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ABSTRACT

Introduction: Neutropenic enterocolitis (NE) consists of ulceration or necrosis of the mucosa of the cecum, terminal ileum, and ascending colon, being a clinical condition caused by an adverse drug event, mainly in chemotherapy regimens. As it is a high mortality rare condition, this report aims to contribute significantly to discussions involving NE and the participation of the multidisciplinary team in the clinical outcome. **Case report**: This is a 75-year-old male patient diagnosed with breast cancer, who developed EN after treatment with adjuvant chemotherapy. The presence of comorbidities and age were the main complicating factors in typhlitis. As it is an important toxicity and can lead to a worsening of the clinical condition of cancer patients, addressing this issue is essential for a faster diagnosis with the possibility of preventive measures. **Conclusion**: Therefore, in view of the notorious increase of cases of NE, the perspective of the qualification of the health team is pointed out, for the inclusion of even more specialized professionals capable of contributing and identifying the signs and symptoms related to hematological toxicities, result of chemotherapy treatments.

Key words: Enterocolitis, Neutropenic/drug therapy; Drug-Related Side Effects and Adverse Reactions; Breast Neoplasms, Male; Chemotherapy, Adjuvant; Patient Care Team.

RESUMO

Introdução: A enterocolite neutropênica (EN) consiste em ulceração ou necrose da mucosa do ceco, íleo terminal e cólon ascendente, sendo uma condição clínica ocasionada como evento adverso de medicamentos, principalmente em esquemas quimioterápicos. Por ser uma condição com alto índice de mortalidade, o presente relato tem como objetivo contribuir significativamente para discussões que envolvem a EN e a participação da equipe multiprofissional no desfecho clínico**. Relato do caso**: Paciente do sexo masculino, 75 anos, com diagnóstico de câncer de mama, evoluindo com EN após tratamento com quimioterapia adjuvante. A presença de comorbidades e a idade foram os principais fatores complicadores do quadro de tiflite. Por ser uma toxicidade importante e que pode levar à piora do quadro clínico do paciente com câncer, abordar esse tema é fundamental para um diagnóstico mais rápido, com possibilidade de medidas preventivas. **Conclusão:** Sendo assim, em virtude do notório aumento dos casos de EN, aponta-se como perspectiva a qualificação da equipe de saúde para a inserção de profissionais ainda mais especializados, capazes de contribuir e identificar os sinais e sintomas relacionados com toxicidades hematológicas, resultado de tratamentos quimioterápicos.

Palavras-chave: Enterocolite Neutropênica/tratamento farmacológico; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Neoplasias da Mama Masculina; Quimioterapia Adjuvante; Equipe de Assistência ao Paciente.

RESUMEN

Introducción: La enterocolitis neutropénica (EN) consiste en la ulceración o necrosis de la mucosa del ciego, íleon terminal y colon ascendente, siendo una condición clínica causada por un evento adverso farmacológico, principalmente en regímenes de quimioterapia. Al tratarse de una afección con una alta tasa de mortalidad, este informe tiene como objetivo contribuir de manera significativa a las discusiones que involucran al EN y la participación del equipo multidisciplinario en el resultado clínico. **Relato del caso:** Paciente masculino, 75 años, diagnosticado de cáncer de mama, que desarrolló EN después del tratamiento con quimioterapia adyuvante. La presencia de comorbilidades y la edad fueron los principales factores de complicación en Tiflite. Como se trata de una toxicidad importante y puede conducir a un empeoramiento de la condición clínica de los pacientes con cáncer, abordar esta cuestión es fundamental para un diagnóstico más rápido con la posibilidad de medidas preventivas. **Conclusión**: Por tanto, ante el notable incremento de casos de EN, se apunta la perspectiva de la calificación del equipo de salud, para la inclusión de profesionales aún más especializados capaces de aportar e identificar los signos y síntomas relacionados con las toxicidades hematológicas, un resultado de los tratamientos de quimioterapia.

Palabras clave: Enterocolitis Neutropénica/tratamiento farmacológico; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Neoplasias de la Mama Masculina; Quimioterapia Adyuvante; Grupo de Atención al Paciente.

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INTRODUCTION

Neutropenic enterocolitis (NE) or typhlitis is a severe complication of neutropenia characterized by segmental ulceration and inflammation with necrosis of the ileum, cecum, and ascending colon; its pathogenesis is poorly understood and probably multifactorial. The main elements in the beginning of the disease appear to be lesion of the intestinal mucosa with neutropenia. These initial conditions lead to intestinal edema and disrupted mucosa surface which becomes more vulnerable to intramural bacterial invasion[1-3].

The utilization of intensive chemotherapeutic regimens has made NE a complication less frequent in oncology therapy in neutropenic patients mostly. Necrotizing enteropathy, typhlitis or ileocecal syndrome were other synonyms used in the literature to describe isolated case reports. Neutropenia-induced immunosuppression combined with chemotherapy toxicity, tumoral infiltration, intramural hemorrhage, and inflammatory reaction lead to direct mucosal injury, up to necrotizing damages and microbial translocation[2,3].

The actual incidence of NE is unknown. A systematic review published in 2005 suggested an incidence of 5.3% in hospitalized adults to treat solid or hematological malignant neoplasms and in patients with bone marrow aplasia. Mortality is approximately 50% in average; it can reach 100% because most of the patients is immunosuppressed[4]. It affects children and adults with severe neutropenia, being a condition initially described in leukemic pediatric patients[3,5].

Immunosuppression condition is a change of the host immune system that leads to the increase of susceptibility to infections; neutropenia predisposes the individual to severe infections. Neutropenic patients are a heterogeneous population needing additional parameters to help to define the actual risk of infection and customize more specific approach to each patient in this category. Risk factors for neutropenia associated infection include advanced age, poor clinical or nutritional performance, low hematologic counting in basal and minimal conditions after the first cycle of high doses chemotherapy[1].

Recognition and early treatment are vital to avoid adverse outcomes. Typically, patients present gastrointestinal symptoms in a context of neutropenia, usually following chemotherapy, with bowel wall thickening and positive microbiological samples[2,6].

Although NE is a clinical condition caused by drugs adverse events, drugs are indispensable inputs in healthcare, it is the most utilized sanitary technology for patients care. They are essential for preserving life and health services, thanks to their prophylactic, curative palliative purposes, or diagnosis. However, its use has risks of sometimes unexpected undesired effects that can cause damages since hospitalization extension, necessity of diagnostic and therapeutic interventions or even death. Drugs safety, efficacy and quality should be considered for these reasons[7].

The current interest in NE is the result of its growth in the adult population as complication of chemotherapy aggressive regimens utilized not only in hematologic neoplasms but also in solid neoplasms. More recently, some cases have been described in association with solid neoplasms, specifically testicles, lungs, colon, breast etc.[8]. It is an important toxicity that can evolve to the worsening of the clinical condition of patient with cancer leading to death, but that it can be treated if discovered early. Based in the explanation, the study has the objective of analyzing a rare case of NE in a patient with solid tumor, in addition to contributing for discussions involving this toxicity significantly and the participation of the health team in the clinical outcome.

Narrative descriptive study, a case report based in information collected from an electronic chart of a patient hospitalized in a philanthropist hospital in Salvador – BA in May 2018 with diagnosis of breast cancer evolving to NE after treatment with adjuvant chemotherapy.

Only the team investigators conducted the search of electronic charts exclusively with data focused to the current report. The Institutional Review Board reviewed and approved the clinical case methodology through report 4.013.581.

CASE REPORT

75-years old male patient, 86 kg, 1.62 m height, hypertense, diabetic, dyslipidemic, chronic renal insufficiency and sedentary. In 2018, noticed node at left breast. Histologic exam revealed invasive ductal carcinoma of moderately differentiated histologic degree (grade 3), the biopsy tumor was tested positive for estrogen and progesterone receptors, expression of positive human epidermal growth factor receptor-type 2 (HER-2), and antigen of cellular proliferation Ki-67 of 30%.

Therefore, it was diagnosed with breast cancer, medical indication of adjuvant treatment with simple mastectomy and chemotherapy with docetaxel (75 mg/m²), carboplatin (AUC 6) and trastuzumab (8 mg/Kg – initial dose and 6 mg/Kg – maintenance dose) repeated at each 21 days, total of six cycles. No breast cancer family history or chemotherapy treatment reported.

At the outpatient unit, after the first day of chemotherapy, returned five days later complaining of pain in long existing "cyst in the neck", formerly painless

and increase of cervical injury volume. The physical exam revealed melena and hypokalemia; in the second day of hospitalization, the occipital pain improved, but with hematochezia. Evolved under infectious and renal surveillance. In the third day, the patient presented hypotension, pain, and abdominal distension; leukogram showed absolute leukopenia with 530/mm³ and absolute neutropenia, grade 4 (170/mm³).

Hemoculture was positive for *Staphylococcus epidermidis*, sepsis and diagnosis of NE. The medical conduct consisted in the introduction of systemic antibiotic therapy and factor of stimulation of colonies of human granulocytes. The patient died in the fourth day of hospitalization associated to NE or typhlitis.

DISCUSSION

Breast cancer is the most common type among women worldwide and in Brazil; after non-melanoma skin cancer, it is accountable for nearly 28% of new cases of cancer in women. Breast cancer also affects men, though rare, representing less than 1% of the total of cases of the disease. Relatively rare before 35 years old, its incidence above this age grows progressively, especially after 50 years of age. Statistics indicate increase of its incidence in developed and underdeveloped countries[9].

Breast cancer treatment is complex and depends of the tumor clinical staging, of the characteristics of the neoplasm and of the patient's clinical condition. Chemotherapy is an alternative treatment indicated frequently, including a large array of antineoplastic drugs, and can be initiated in neoadjuvant, adjuvant or metastatic contexts. Neoadjuvant chemotherapy is known as primary or preoperative, being utilized by patients with locally advanced breast cancer and operable whose main objective is to reduce the primary tumor and ensure the integrity of the breast. Adjuvant chemotherapy is utilized after the surgical procedure with curative intent and together with hormone therapy in selected cases, prolongs the patient's survival; the main chemotherapics utilized for breast cancer treatment are anthracyclines and taxanes[10,11].

The chemotherapy protocol proposed for the patient with carboplatin, docetaxel and trastuzumab was mentioned in a case report where a woman with HER-2 breast cancer treated with this regimen evolved to severe neutropenia[12]. In another clinical study conducted with 50 Japanese women with diagnosis of breast cancer in treatment with this same protocol, 18.36% presented hematologic toxicity and for 34% the dose was reduced, or the treatment discontinued because of adverse reactions[13]. Therefore, the chemotherapic regimens most frequently associated to neutropenia were combinations of platinum and taxanes (carboplatin and docetaxel; carboplatin, docetaxel and trastuzumab; carboplatin and nab-paclitaxel), which connects the relation of the chemotherapeutic treatment of the patient in question with the toxicity[5,11].

Despite the continuous evolution of infection prevention, febrile neutropenia remains as a frequent complication in oncologic patients and is a limiting factor in the administration of the antineoplastic systemic therapeutic. As the gastrointestinal mucosa system is formed by epithelium in constant proliferation, they are more affected also by antineoplastic cytotoxic therapeutic[14]. It is uncommon to find NE in patients with breast cancer. The period of neutropenia related to chemotherapy is generally short for these patients. However, in the last years, the condition has been reported in patients submitted to taxanes-based chemotherapy. It is known that these agents have great potential for causing extensive inflammatory alterations of the mucosa[5].

After hospitalization, the patient evolved with pain and abdominal distention, in addition to hematochezia and melena. Some authors[6,3] reported that NE clinical characteristics include fever and abdominal pain, but abdominal distention, swelling and diarrhea were reported too as associated signs and symptoms. Typically, melena or hematochezia are less common forms of presentation, which makes early diagnosis difficult to determine with well-defined therapeutic conducts.

And because of its unspecified presentation, NE can imitate many other diagnosis, but the confirmation generally involves findings of fever, abdominal pain, neutropenia and thickening of abdominal wall. Typically, although this condition occurs in patient severely immunosuppressed or myelosuppressive with leukemia, it was observed too in individuals with other advanced neoplasms who received immunosuppressive chemotherapy[5].

The evolution of the condition was suggestive of NE, being initiated treatment with broad spectrum antimicrobial and growth factor. NE management appears to be controversial and because of the improvement of the support care, studies[2,3,5] reported the success of non-surgical treatment. The consensus is immediate administration of antibiotics that should cover gram-positive, gram-negative, and anaerobic pathogens. Other studies[3,5,12] also suggest the advantage of using stimulating factor of colonies of granulocytes in neutropenic patients with sepsis or shock.

In the case of the patient in question, the presence of comorbidities and age were the main complication factors of neutropenia and the clinical outcome was death. The risk of severe complications depends of the duration of

neutropenia (>7 days), of the presence of comorbidities, as liver or renal dysfunction, age >60 years mainly; and among the main clinical situations encountered in severely ill neutropenic patients, gastrointestinal infections were the most frequent for 31%, followed by respiratory in 30%[15].

With the increasingly sophisticated chemotherapeutic regimens, its use improved cancer survival rates significantly. Concern with the quality of life of these patients is paramount because of the treatment-related adverse events and the symptoms associated to the disease. As NE is a rare toxicity with high rate of mortality the multi-professional team must be prepared to identify signs and symptoms and offer treatment options to achieve improvement of the quality of life[16].

CONCLUSION

NE is a rare clinical condition of difficult diagnosis and lethal. Patients in chemotherapy treatment are more propense to severe leukopenia conditions and consequently evolve to NE. It should be emphasized the necessity of further discussions about the theme as early diagnosis is essential to optimize the therapeutic measures.

Although the clinical outcome of this case has not been favorable, the findings of the current study allowed to contribute significantly for the clinical decision and improve the indicators associated to the high rate of mortality of typhlitis. Because of the notorious increase of cases of NE, the perspective is the qualification of the health team to include more skilled professionals able to contribute and identify signs and symptoms related with hematological toxicities resulting from chemotherapeutic treatments.

CONTRIBUTIONS

Luana Santana Bacelar, Martamaria de Souza Ferraz Ribeiro and Maria Teresita Bendicho contributed for the study conception and/or design, collection, analysis and interpretation of the data, wording, and critical review. Rosa Malena Fagundes Xavier, Elisama Andrade Miranda and Caroline Chagas Lopes contributed for the wording and critical review with intellectual contribution. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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