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LETTER TO EDITOR

Successful Treatment of Sinusitis with Topical Human Milk in a Lymphoma Patient Using Rituximab

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To the Editor,

Chronic respiratory infections are frequent manifestations in patients with both primary and secondary antibody deficiencies due to their poor production of serum and secretory immunoglobulins. Intravenous immunoglobulin (IVIg) replacement treatment usually reduces susceptibility to infections, although it is well-known that IVIg does not reach mucosae in significant amounts.

Human milk, a major source of secretory IgA (SIgA), also contains several other anti-infectious factors, which interact among themselves and with infant digestive and upper respiratory tract mucosa, providing effective passive immunity [1]. Therapeutic uses of human milk have been anecdotal, and, as far as we could find in medical literature, this is the first report of human milk used as nasal adjuvant therapeutic proposal in a lymphoma patient with hypogammaglobulinemia due to rituximab treatment.

After informed consent and discussion with ethics committee colleagues as a compassionate therapy, and especially considering its safety and lack of side effects, we decided to administer human milk serum intranasally to a 76-year-old woman with non-Hodgkin lymphoma, diagnosed in 2007 (see Fig. 1). After several rituximab cycles, she presented with persistent hypogammaglobulinemia (very low serum IgG levels, undetectable IgM and IgA, as well as salivary IgA) and extremely low peripheral B lymphocytes (0.01%). The patient also presented chronic pansinusitis, having been treated several times with antibiotics without significant and long-lasting response. Regular IVIg administration in adequate doses (400 mg/kg), every 4 weeks, maintained IgG levels above 700 mg/dL (latest Ig levels as follows: IgG, 819 mg/dL, IgM, 9 mg/dL, IgA, < 7 mg/dL, and IgE, < 2 kU/L). Despite this, she went on requiring frequent antibiotic treatments due to recurrent sinusitis without significant response. Due to the persistence of clinical manifestations and poor quality of life, particularly poor sleep quality and lack of appetite, we decided to introduce breast milk by the nasal cavity as an attempt to provide her with topical secretory IgA to improve upper respiratory symptoms.

The milk was obtained from healthy donors from middle- to high-income status at a nonprofit human milk bank located in a maternity hospital (Hospital e Maternidade Santa Joana, São Paulo). All donors had negative serology for HIV, hepatitis B and C, CMV, rubella, syphilis, and toxoplasmosis. The milk had been donated aiming to feed premature babies and we received leftover milk. Milk collection was performed at the hospital by a nurse under strict hygienic conditions, and all the samples were submitted to pasteurization. In our laboratory facilities, always working under sterile conditions, the received pooled milk samples were submitted to centrifugation at a low temperature to separate the fat and cellular layers, which were discarded, and the milk serum was then submitted to a second pasteurization (62.5 °C for 30 min). Total protein and IgA contents were determined by conventional techniques. The concentration of the solution was adjusted with sterile 0.9% NaCl to 14.4 mg/dL of the total IgA and to 5.95 mg/mL of the total protein content, and the final solution tested negative for bacterial and fungus growth. The solution was frozen (− 20 °C) in 2 mL individual doses until use. No preservative substances were added and the mildly cloudy solution was odorless and tasted similar to the saline vehicle.

It was recommended to the patient to maintain the material at − 20 °C and to use 1 mL of the breast milk solution in each

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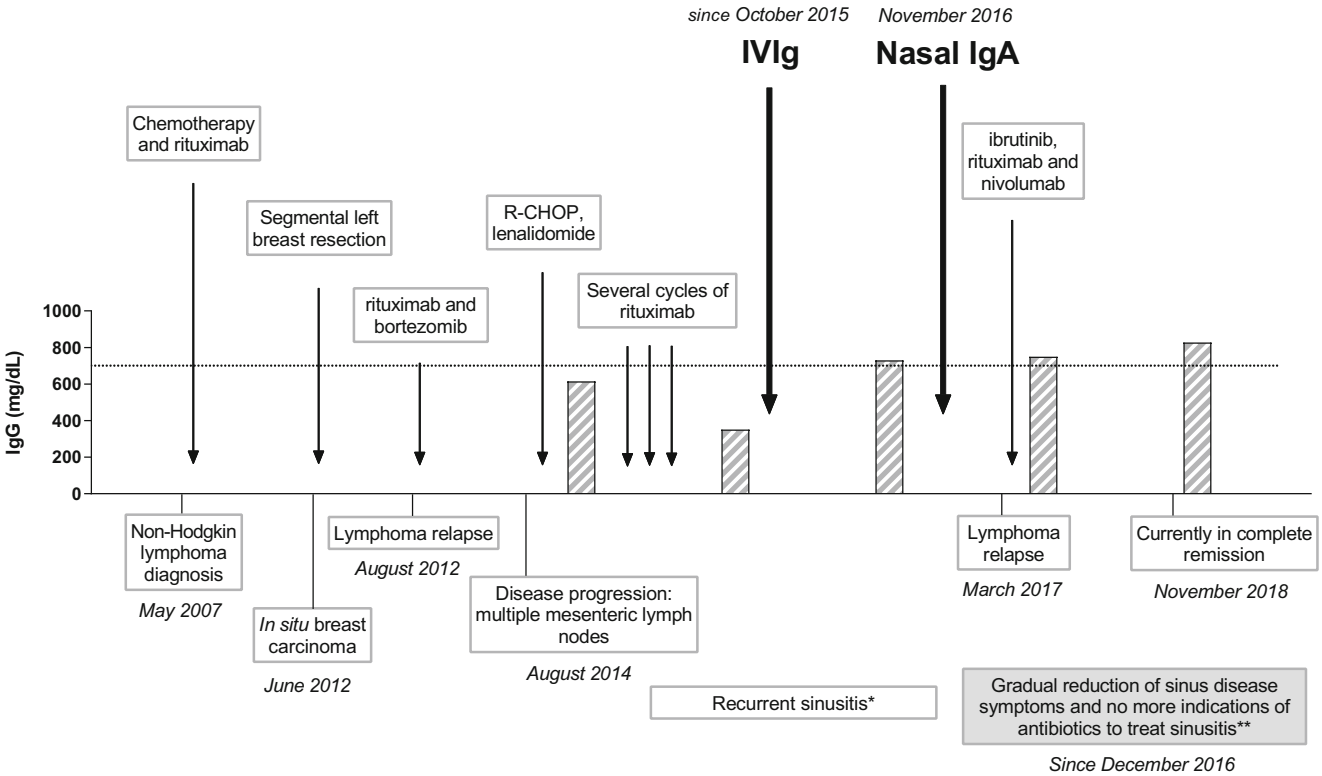

Fig. 1 Timeline of clinical evolution and treatment of the patient here described. R-CHOP: combined immune chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. *Six recurrent sinus infections with antibiotics treatment from October 2014 to November 2016. **Significant reduction of cough, postnasal discharge, headache, and improvement of overall quality of life

nostril three times a day after carefully removing nasal secretions with sterile 0.9% NaCl solution at 37 °C. Approximately 15 days after the introduction of the human milk supernatant, the patient has no longer indication to treat sinusitis with antibiotics, and over time, she also reported a significant reduction in cough, nasal secretion and postnasal discharge, and an improvement of sleep, appetite, and overall quality of life. A relevant point is that the patient could increase her social activities, being the closer contact with her grandchildren, a particularly pleasant aspect of such activities. Thus far, she has received the preparation for 24 months, has not reported any side effects, and currently uses the human milk serum only twice a day. The patient had a progression of lymphoma to the abdominal lymph nodes that had a complete response with anti-PD-L1 checkpoint inhibitors combined with rituximab; later, she had a meningeal infiltration of lymphoma that started responding to a local treatment of methotrexate/cytarabine combined with the systemic treatment.

In the literature, there are only few reports on the use of immunoglobulins to treat mucosal infections, all of which were published some decades ago. Eibl et al., in 1988 [2], reported that oral administration of an immunoglobulin preparation (IgAbulin®, Immuno AG, Vienna, Austria, containing 73% serum IgA and 26% IgG) was employed to prevent necrotizing enterocolitis in low-birth-weight infants and in the treatment of a patient with toxin-producing *Clostridium difficile* enteritis who completely recovered [3]. Nasal administration of the same preparation was successfully employed to prevent infections in patients with hypogammaglobulinemia [4] and to decrease the frequency of upper respiratory tract infections (URTI) in cross-country skiers [5]. However, no significant decrease in URTI was observed when the preparation was used as nose-drops for world-class canoeists [6].

On the other hand, we did not find studies with secretory IgA, whose main source in humans is colostrum and milk. Responsible for the production of milk IgA, plasma cells in the mammary gland lamina propria originate from B lymphocytes predominantly primed in other mucosal sites, particularly in the gut and respiratory tract; thus, human milk has high SIgA levels reactive with several mucosal pathogens [1]. Additionally, SIgA has been shown to have anti-inflammatory properties.

In addition to SIgA, that reaches an average of 20 g/L in the first days of lactation, human colostrum and milk contain high concentrations of various other soluble factors with anti-infectious activity, such as other immunoglobulin classes (IgM and IgG in lower concentrations), enzymes (lysozyme, peroxidase), lactoferrin, oligosaccharides, cytokines, and nucleotides [1]. In general, the concentrations of these factors are not affected by pasteurization [7], and these factors should also have contributed to the control of chronic sinusitis in the patient described here.

This case represents a preliminary observation showing that the topical use of breast milk serum containing SIgA and other anti-infectious factors could be an adjuvant treatment for hypogammaglobulinemia and/or agammaglobulinemia patients, including oncologic patients with chronic upper respiratory infections. Thus, the implementation of intranasal therapy with human milk may represent an innovative approach aimed at preventing and reducing the morbidity of respiratory infections in immunosuppressed individuals.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

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