Hypogammaglobulinemia and rituximab: case reports

Hipogamaglobulinemia e rituximabe: relato de casos

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ABSTRACT

Secondary immunodeficiency can result from neoplasms, infections, or immunosuppressive therapy. Rituximab (RTX) is an anti-CD20 antibody that depletes B lymphocytes and can induce symptomatic hypogammaglobulinemia. We report 3 cases of symptomatic hypogammaglobulinemia associated with the use of RTX. In patient 1 with rheumatoid arthritis, RTX induced low levels of immunoglobulins and recurrent airway infections. RTX discontinuation led to a normalization of the humoral immune response. Patients 2 and 3, treated with RTX for non-Hodgkin lymphoma and systemic lupus erythematosus, respectively, developed persistent secondary hypogammaglobulinemia requiring immunoglobulin replacement therapy for years. After RTX discontinuation, patients may experience rapid recovery of humoral function or remain with low serum immunoglobulin levels for extended periods. With the increasing use of therapies targeting components of the immune system, a high degree of clinical suspicion for the development of secondary immunodeficiency may minimize the morbidity and mortality associated with these therapies.

Keywords: Rituximab, rheumatoid arthritis, antibiotic prophylaxis.

RESUMO

As imunodeficiências secundárias podem ser uma consequência de neoplasias, infecções ou tratamentos imunossupressores. O rituximabe (RTX) é um anticorpo anti-CD20 que depleta os linfócitos B e pode induzir uma hipogamaglobulinemia sintomática. Aqui, relatamos três casos de hipogamaglobulinemia sintomática associada ao uso de RTX. Na primeira paciente com artrite reumatoide, o RTX induziu a baixos níveis de imunoglobulinas associadas a infecções de vias aéreas de repetição. Após a suspensão do RTX, houve normalização da resposta imune humoral. Os outros dois casos, com o uso de RTX para tratamento de linfoma não-Hodgkin e lúpus eritematoso sistêmico, respectivamente, as pacientes evoluíram com hipogamaglobulinemia secundária persistente, com necessidade de reposição de imunoglobulina por vários anos. Pacientes tratados com RTX podem apresentar, após a sua suspensão, uma recuperação rápida da função humoral ou permanecerem com baixos níveis séricos de imunoglobulinas por longos períodos. Com o crescente uso dos tratamentos direcionados para componentes do sistema imunológico, um alto grau de suspeição clínica para o aparecimento de imunodeficiências secundárias pode minimizar a morbimortalidade associada a estes tratamentos.

Descritores: Rituximab, artrite reumatoide, antibioticoprofilaxia.

Introduction

Immunodeficiencies, conditions that affect correct functioning of the immune system, can be classified as primary, recently renamed as "inborn errors of immunity", or secondary. Secondary immunodeficiencies can occur due to underlying diseases, such as neoplasia, infection, or immunosuppressive treatment. Secondary immunodeficiencies are more prevalent than primary immunodeficiencies and often go unrecognized by clinicians.[1]

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B lymphocyte disorders are the most common subtype of immunodeficiency, responsible for approximately 50% of diagnosed primary immunodeficiencies. They are characterized by increased susceptibility to bacterial respiratory tract infections, particularly those due to *Streptococcus pneumoniae* and *Haemophilus influenzae*. Symptoms include recurrent sino-pulmonary infections, such as otitis media, sinusitis, and pneumonia. Diarrhea, fatigue, autoimmune manifestations (particularly cytopenia), and hearing loss are also common. Patients with humoral immunodeficiency have decreased or absent serum immunoglobulin levels, but may have normal or increased levels with abnormal function.[2-4]

In 1997, rituximab (RTX), an anti-CD20 monoclonal antibody, was the first antibody to be approved for relapsed or refractory CD20+ follicular or low-grade B-cell non-Hodgkin lymphoma. Its use was then extended to other B-cell malignancies and to non-malignant diseases such as rheumatoid arthritis. Using RTX to deplete B lymphocytes in patients with rheumatoid arthritis, either as monotherapy or in association with cyclophosphamide and/or corticosteroids, has been part of the therapeutic arsenal since 1998.[3]

The binding of RTX to CD20 may result in B lymphocyte apoptosis through mechanisms that are not yet fully understood. RTX binding can also activate the classic complement pathway, resulting in membrane attack complex and cell lysis. Additionally, it recruits natural killer cells by binding to FcɤRII, which leads to antibody-mediated cellular cytotoxicity and,

finally, macrophages phagocytose the target cell by recognizing RTX- bound CD20.[3] After RTX treatment, around 38.5% of patients have low IgG levels, and sino-pulmonary infections occur in an average of 6.6%. Immunoglobulin replacement appears to reduce the frequency of infections.[4] Although the depletion of immunoglobulin M (IgM) after RTX treatment is more frequent and prolonged than that of IgG, it is less clinically significant.[5] Here, we present and discuss 3 cases of hypogammaglobulinemia associated with RTX treatment in the context of lymphoma or autoimmune disorders.

Presentation of the cases

Case 1

V.F.P.D., a 47-year-old woman, has been diagnosed with rheumatoid arthritis for 11 years. After several therapeutic regimens with little response, RTX was initiated, which led to symptom control. Six months after initiating RTX, the patient began experiencing recurrent acute sinusitis, a total of 5 episodes in the last 12 months, with subsequent chronification and recurrent pneumonia (5 episodes during the same period) (Table 1). She reported 2 hospitalizations in the last month, in which intravenous broad-spectrum antibiotics (meropenem) were used to treat pneumonia. Computed tomography of the paranasal sinuses (Figure 1A and 1B) and chest (Figure 2A and 2B) performed between infections showed pansinus involvement and bronchiectasis, respectively. She did not present with lower respiratory symptoms;
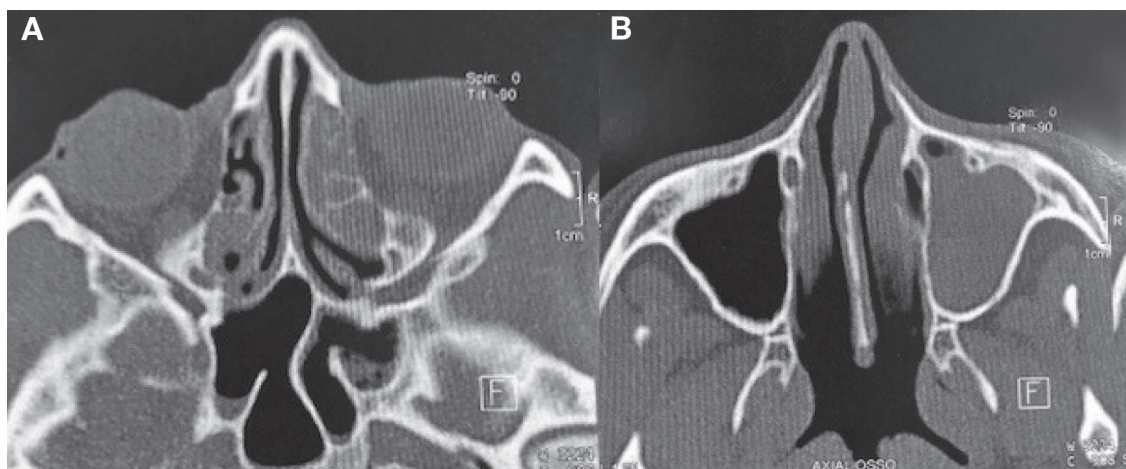
Figure 1
Computed tomography of the paranasal sinuses. Axial section showing diffuse haziness of ethmoid cells and the right maxillary sinus, as well as secretion in the sphenoid sinuses

pulmonary auscultation showed no changes, although a moderate amount of bilateral mucopurulent rhinorrhea was observed in the initial assessment.

Regarding family history, she has a maternal aunt diagnosed with rheumatoid arthritis. The laboratory test results (reference values [RV] for age) were: IgM: 25 mg/dL (RV: 33–293), IgG: 593 mg/dL (RV: 739–1390), IgA: 129 mg/dL (RV: 65–421), IgE: 46.2 kU/L (≤ 140 kU/L), serum protein electrophoresis: gamma globulin 8.8%-0.55 g/dL (10.3%-18.2%, 0.74-1.75 g/dL)(Table 2); other routine tests were normal.

Immunophenotyping of lymphocyte subpopulations showed a lack of B lymphocytes (CD19) and < 1% of peripheral blood lymphocytes; other cell types were normal (see Table 3). Once hypogammaglobulinemia secondary to RTX treatment was diagnosed, prophylactic antibiotic therapy with sulfamethoxazole/trimethoprim was initiated at 800/160 mg twice a day, and intravenous human immunoglobulin (IVIG) replacement was indicated. IVIG was prescribed at an immunomodulatory dose by the attending rheumatologist: 2 g/kg of weight for the first application.

Table 1
Clinical course of the cases

	Sex/ Age	Previous diagnosis	Chemo-immuno-therapy	Time of RTX use until ID diagnosed	Symptoms	Serum IgG level in ID diagnosis	Treatment, etc.	Current serum IgG level
Case 1	♀, 47 years	Rheumatoid arthritis	RTX	6 months	Acute sinusitis and recurrent PNM	593 mg/dL (RV 739-1390 mg/dL)	RTX suspended. Tofacitinib prescribed. IVIG: 2 g/kg every 28 days, being suspended 10 months later. ATB: SMX/TMP	1025 mg/dL (RV 739-1390 mg/dL) 3 months after start
Case 2	♀, 32 years	Systemic lupus erythematosus	RTX	3 years	Sinusitis, acute otitis and recurrent PNM	698 mg/dL (RV 739-1390 mg/dL)	RTX suspended. HQC + MTX prescribed IGIV: 400 mg/kg every 28 days ATB: SMX/TMP	855 mg/dL (RV 739-1390 mg/dL)
Case 3	♀, 48 years	Non-Hodgkin lymphoma	RTX	1 year	Sinusitis, acute otitis, and recurrent PNM	623 mg/dL (RV 952-1538 mg/dL)	RTX suspended. IGIV: 416 mg/kg every 28 days	1112 mg/dL (RV 739-1390 mg/dL) 5 months after start

ATB = antibiotic, HQC = hydroxychloroquine, ID = immunodeficiency, IgG = Immunoglobulin G, IGIV = intravenous immunoglobulin, PNM = pneumonia, RTX = rituximab, RV = reference value, SMX = sulfamethoxazole, TMT = trimethoprim.
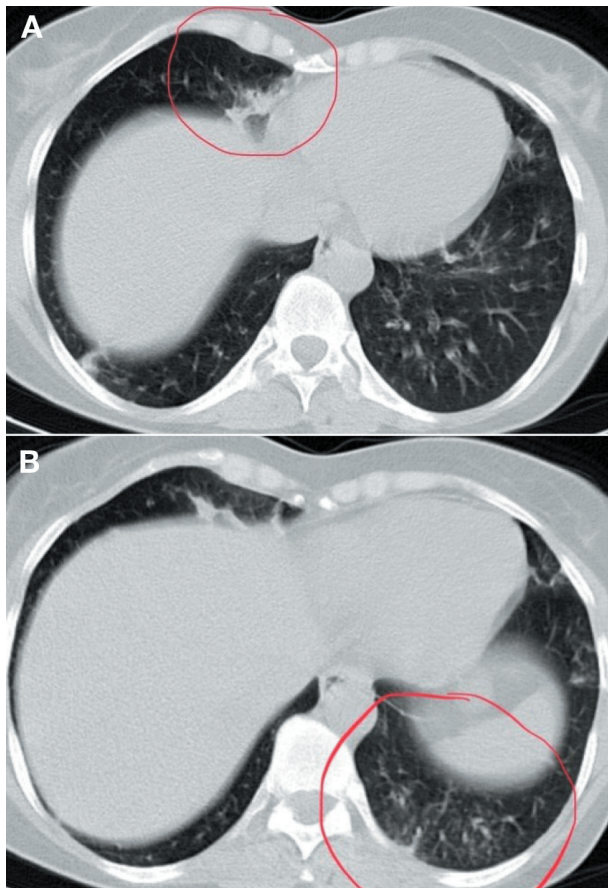
Figure 2

Chest computed tomography showing bronchiectasis in the lingula and mucus stasis in peripheral bronchioles

The rheumatologist preferred to suspend RTX and prescribe tofacitinib. Approximately 3 months after the initial consultation and 1 month after RTX had been suspended and IVIG therapy had begun, total serum IgG (1025 mg/dL) normalized. Since then (> 10 months of follow-up), the patient has had no further infectious conditions. Her rheumatoid arthritis remains controlled and antibiotic prophylaxis with sulfamethoxazole/trimethoprim was suspended after serum IgG levels normalized (Table 2). Radiological findings indicated normalized sinuses and improved lung condition (Figures 3A and 3B).

Case 2

J.T.V., a 48-year-old woman with non-Hodgkin lymphoma, was treated with chemotherapy and RTX in 2012. About a year after using RTX, she began having recurrent infections, including several pneumonias, otitis, and sinusitis, requiring antibiotic

therapy (Table 1). Tomography of the facial sinuses showed pansinus mucosal thickening (Figure 4A and 4B). In December 2018, she was referred to the immunology service, where she was diagnosed with hypogammaglobulinemia (Table 2).

Laboratory tests performed that month showed IgA: < 6.4 mg/dL (RV 153-359 mg/dL), IgE: < 4.3 mg/dL (RV < 100 mg/dL), IgG: 623 mg/dL (RV 952-1538 mg/dL), and IgM: 17.5 mg/dL (RV 73-171 mg/dL). Immunophenotyping of lymphocyte subpopulations revealed a lack of B lymphocytes (Table 3). Serology for pneumococci from January 2019: serotype 4: < 0.5, serotype 6b: < 0.5, serotype 9v: < 0.5, serotype 14: 3.4, serotype 18c: < 0.5, serotype 19f: 1.2, and serotype 23f: < 0.5.
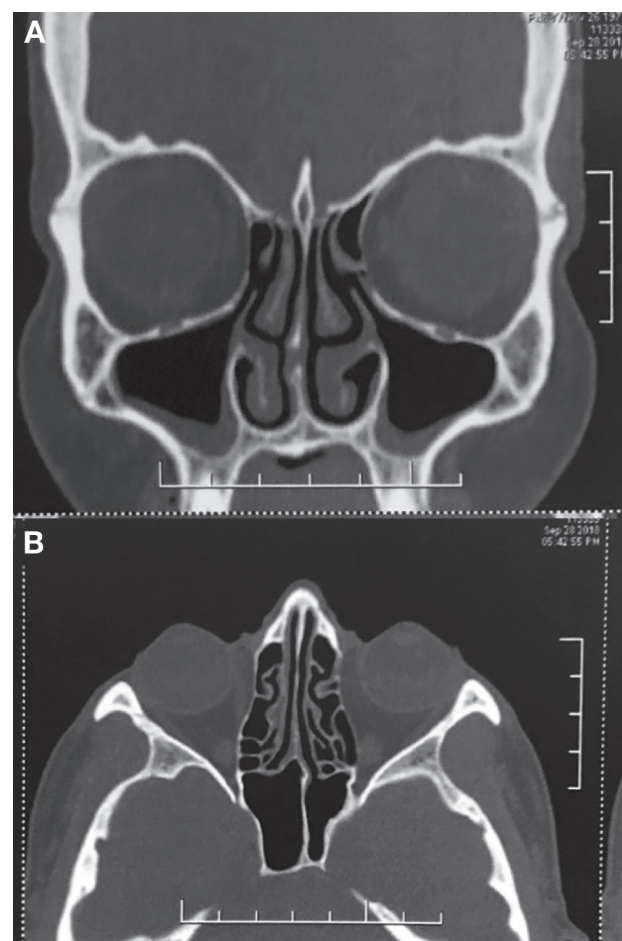
Figure 3

Computed tomography of the paranasal sinuses 6 months after the first exam (Figure 1) showing normalization of the sinus disease. Mild non-specific thickening of the mucus persists on the maxillary sinus floor

Table 2

Serial immunoglobulin dosage

	Serum IgG level at ID diagnosis	Serum IgG level at follow-up	Current serum IgG level
Case 1	593 mg/dL (RV 739-1390 mg/dL)	–	1025 mg/dL (RV 739-1390 mg/dL)
Case 2	698 mg/dL (RV 739-1390 mg/dL)	798 mg/dL (RV 739-1390 mg/dL)	855 mg/dL (RV 739-1390 mg/dL)
Case 3	623 mg/dL (RV 952-1538 mg/dL)	564 mg/dL (RV 952-1538 mg/dL)	1112 mg/dL (RV 739-1390 mg/dL)

ID = immunodeficiency, IgG = Immunoglobulin G, RV = reference value.

Immunoglobulin measurements were repeated in February 2019, showing IgG: 623 mg/dL, IgE: < 4.3 mg/dL, IgM: < 17.5 mg/dL, and IgA: < 6.4 mg/dL; immunophenotyping confirmed a lack of B cells (Table 3). In May 2019, due to symptomatic hypogammaglobulinemia and the lack of B cells,

IVIG was initiated at a dose of 25 g (416 mg/kg) every 28 days, after which the patient presented no further symptoms or infections and required no antibiotic therapy. A new immunoglobulin dose was administered in July 2019 (ie, 2 months after starting IVIG), with the following results: IgE: < 2 mg/dL, IgA:
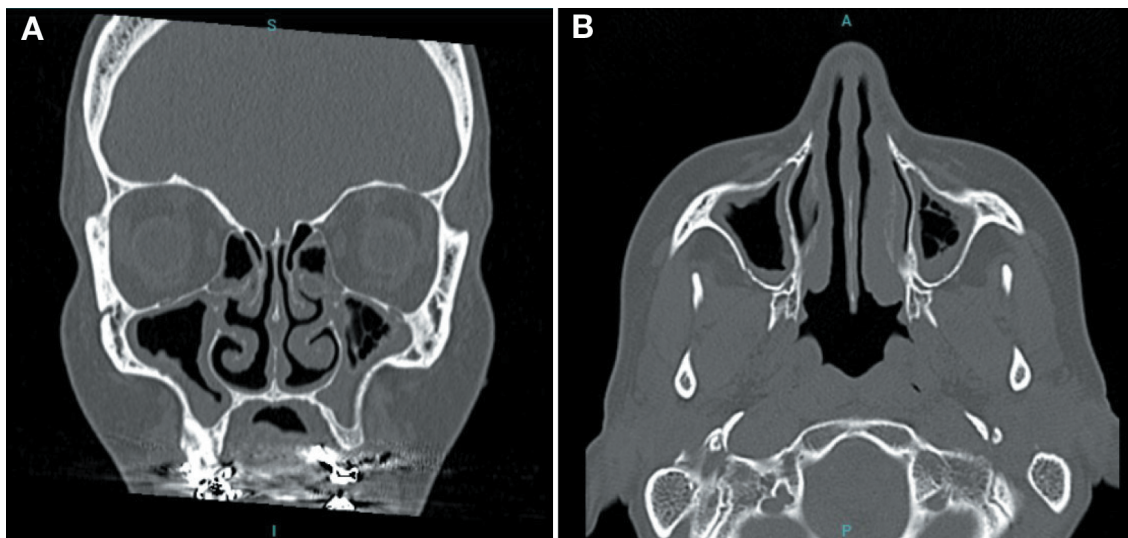
Figure 4

Computed tomography of facial sinuses from September 2014 (coronal and axial sections) demonstrating bilateral thickening of the mucus and some ethmoid cells

< 10 mg/dL, IgG: 1112 mg/dL, and IgM: < 20 mg/dL. Since the B lymphocyte deficiency in peripheral blood persisted in new immunophenotyping (Table 3) in January 2020, immunoglobulin replacement with IVIG was continued at the same dose, pending further follow-up.

Case 3

P.R.V.F., a 32-year-old woman, was initially diagnosed with relapsing polychondritis approximately 10 years ago and was treated with methotrexate and prednisone. Three years later, due to oral and esophageal ulcers, polychondritis of the small and

Table 3

Serial immunophenotyping of peripheral blood lymphocytes

	Case 1	Case 2	Case 3
Immunophenotyping at diagnosis	CD3: 1959 cells/mm^3 (RV 100-3900 cells/mm^3)	CD3: 2393 cells/mm^3 (RV 849.1-1963.3 cells/mm^3)	CD3: 1238 cells/mm^3 (RV 849.1-1963.3 cells/mm^3)
	CD19: 2 mm^3 cells/mm^3 (RV 90-680 cells/mm^3)	CD19: 54 cells/mm^3 (RV 124.2-415.9 cells/mm^3)	CD19: 0 cells/mm^3 (RV 124.2-415.9 cells/mm^3)
	CD4: 1126 cells/mm^3 (RV 560-2700 cells/mm^3)	CD3/CD4: 1479 cells/mm^3 (RV 477.5-1140.8 cells/mm^3)	CD3/CD4: 411 cells/mm^3 (477.5-1140.8 cells/mm^3)
	CD8: 1047 cells/mm^3 (RV 211-724 cells/mm^3)	CD3/CD8: 860 cells/mm^3 (RV 211.7-724.6 cells/mm^3)	CD3/CD8: 602 cells/mm^3 (RV 211.7-724.6 cells/mm^3)
	CD56: 320 cells/mm^3 (RV 87-760 cells/mm^3)	CD56: 134 cells/mm^3 (RV 137-567.8 cells/mm^3)	CD56: 29 cells/mm^3 (RV 137-567.8 cells/mm^3)
	CD4/CD8: 1.26 cells/mm^3 (RV 1.2-4.5 cells/mm^3)	CD4/CD8: 1.71 cells/mm^3 (RV 1.2-4.5 cells/mm^3)	CD4/CD8: 0.68 cells/mm^3 (RV 1.2-4.5 cells/mm^3)
Immunophenotyping after suspending rituximab	–	CD3: 1458 cells/mm^3 (RV 849.1-1963.3 cells/mm^3)	CD3: 1192 cells/mm^3 (RV 849.1-1963.3 cells/mm^3)
		CD19: 281 cells/mm^3 (RV 124.2-415.9 cells/mm^3)	CD19: 54 cells/mm^3 (RV 124.2-415.9 cells/mm^3)
		CD3/CD4: 689.1 cells/mm^3 (RV 477.5-1140.8 cells/mm^3)	CD3/CD4: 331 cells/mm^3 (RV 477.5-1140.8 cells/mm^3)
		CD3/CD8: 726 cells/mm^3 (RV 211.7-724.6 cells/mm^3)	CD3/CD8: 783 cells/mm^3 (RV 211.7-724.6 cells/mm^3)
		CD56: 86 cells/mm^3 (RV 137-567.8 cells/mm^3)	CD56: 55 cells/mm^3 (RV 137-567.8 cells/mm^3)
		CD4/CD8: 0.94 cells/mm^3 (RV 1.2-4.5 cells/mm^3)	CD4/CD8: 0.42 cells/mm^3 (RV 1.2-4.5 cells/mm^3)

RV = reference value.

large joints and malar erythema, associated with laboratory changes, such as increased C-reactive protein and positivity for antinuclear factor and anti-DNA antibodies, she was diagnosed with systemic erythematosus lupus. After tocilizumab therapy failed, RTX was introduced, leading to significant symptomatic improvement after 3 months.

The patient began experiencing severe recurrent respiratory infections approximately 3 years after RTX treatment began, one of which required admission to intensive care for sepsis secondary to sinusitis. Over the next 4 years, she experienced 25 episodes of sinusitis and 2 episodes of pneumonia (Table 1). Laboratory tests performed approximately 3 years after RTX treatment began showed B lymphocyte depletion, as well as hypogammaglobulinemia (Tables 2 and 3): IgG: 698 mg/dL (RV: 739-1390), IgA: 57 mg/dL (RV: 65-421), and IgM: 22 mg/dL (RV: 33-293; CD20 B lymphocytes: 54 cells/mm3 (90-680 mm3). At that point it was decided to suspend RTX and switch to hydroxychloroquine associated with methotrexate. After 2 years of sustained infections, antibiotic prophylaxis was begun with sulfamethoxazole/trimethoprim, which did not prevent new infections. IVIG replacement was then initiated at a dose of 400 mg/kg every 28 days. Six months after the first dose of IVIG, suspension was attempted, but her immunoglobulin levels continued to decline progressively, despite normalization of B lymphocytes. IVIG replacement was restarted at the previous dose and common variable immunodeficiency was suspected.

Discussion

In this case report, we evaluated 3 women in the third or fourth decade of life, 2 of whom had autoimmune diseases (rheumatoid arthritis [Case 1] and systemic lupus erythematosus [Case 3]), and the other had a neoplasm (non-Hodgkin lymphoma [Case 2]).

At some point in their treatment, all 3 patients used RTX, a chimeric anti-CD20 monoclonal antibody. This medication depletes B lymphocytes, but only 38.5% of patients present hypogammaglobulinemia and approximately 6.6% present symptomatic hypogammaglobulinemia[5], which is clinically expressed as recurrent sino-pulmonary infection. Despite recurrence, these common infections are caused by typical germs. Thus, diagnosis of secondary symptomatic hypogammaglobulinemia may be late, ie, when the patients already have sequelae, such as bronchiectasis, as in Case 1. To avoid such complications, a high degree of clinical suspicion is necessary. Symptomatic hypogammaglobulinemia occurred in all 3 patients. After the diagnosis, IVIG replacement therapy was performed (at an immunomodulatory dose in Case 1 and a replacement dose in Cases 2 and 3).

In Case 1, to avoid treatment with 2 high-cost medications, the rheumatologist replaced RTX with a different therapeutic regimen to control the underlying rheumatoid arthritis. In this case, IgG levels normalized after RTX was suspended and the therapeutic regimen was changed. The patient had no new infections by the end of follow-up. This patient was monitored in a private practice and lived in a distant city. Furthermore, at one point her health insurance lapsed, which made it impossible to carry out laboratory tests. Similar impediments to testing occurred in Cases 2 and 3, who were monitored in a public health unit.

In Case 3, after suspending RTX, the immunoglobulin levels did not normalize and the patient had an autoimmune disease, so a diagnosis of common variable immunodeficiency was suggested. Common variable immunodeficiency is the most common primary immunodeficiency in adults. B lymphocyte dysfunction leads to low serum IgG levels and, usually, IgA and/or IgM. As a consequence, patients can develop recurrent bacterial airway infections (often later in life). Other clinical disorders have been widely described, such as chronic enteropathy, malignant or benign lymphoproliferative diseases, granulomatous diseases, and autoimmune disorders.[6-8] Thus, although the recurrent respiratory infections may have been due to common variable immunodeficiency rather than RTX treatment, the patients continue with IVIG replacement and no longer suffer them. Although recurrent infection is the main presentation of primary immunodeficiency, autoimmunity is also a factor, often due to loss of self-tolerance.[9]

In the Case 2, due to persistent hypo-gammaglobulinemia, IVIG replacement continued for several years after suspending RTX treatment for non-Hodgkin lymphoma. Barmettler et al. classify patients with post-RTX hypogammaglobulinemia into 2 subgroups: (1) normal immunoglobulin and B lymphocyte recovery, and (2) persistent symptomatic hypogammaglobulinemia. In the latter group, there is an increased risk of infection due to humoral dysfunction/deficiency and these patients may benefit

from IVIG replacement.[6] Case 2 probably belongs to this group.

Case 1 probably belongs to the first subgroup due to the rapid recovery of immunoglobulin and B lymphocyte levels, whereas Case 2 may belong to the persistent hypogammaglobulinemia subgroup. The average duration of IVIG replacement therapy in the persistent hypogammaglobulinemia subgroup is 83 months after RTX is suspended, compared to an average of 24 months in the normal recovery subgroup.[6] This is why in Case 3, even though other immunoglobulin classes decreased, common variable immunodeficiency still could not be diagnosed conclusively. It can be challenging to distinguish patients with sustained hypogammaglobulinemia from those with primary immunodeficiencies, especially common variable immunodeficiency.[10]

Conclusions

In these 3 cases, the patients developed humoral immunodeficiency, which, if not diagnosed in time, can have severe clinical repercussions. In Cases 1 and 3, there was a significant delay between the onset and diagnosis of humoral immunodeficiency syndrome. In Case 1, the pulmonary sequelae proved irreversible even after adequate treatment. With the development of new monoclonal antibodies for a wide variety of diseases, especially in patients who use anti-B lymphocyte antibodies, a high degree of clinical suspicion is necessary regarding symptomatic secondary hypogammaglobulinemia, initiating antibiotic prophylaxis and, if necessary, immunoglobulin replacement therapy.

References

1. Kaplan B, Bonagura VR. Secondary hypogammaglobulinemia: an increasingly recognized complication of treatment with immunomodulators and after solid organ transplantation. Immunol Allergy Clin North Am. 2019;39(1):31-47.

2. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract. 2016:4(1):38-59.

3. Tangye SG, Waleed Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human inborn errors of immunity: 2019 update on classification from International Union of Immunological Societies expert committee. J Clin Immunol. 2020;40(1):24-64.

4. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol. 2020;40(1):66-81.

5. Pierpont TM, Limper CB, Richards K. Past, present and future of rituximab – the world's first monoclonal antibody therapy. Front Oncol. 2018;8:163.

6. Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, Infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMA Netw Open. 2018:1(7):e184169.

7. Boileau J, Mouillot G, Gérard L, Carmagnat M, Rabian C, Oksenhendler E, et al. Autoimmunity in common variable immunodeficiency: Correlation with lymphocyte phenotype in French DEFI study. J Autoimmun. 2011;36(1):25-32.

8. Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. Ann Allergy Asthma Immunol. 2019;123(5):454-60.

9. Hoyos-Bachiglu R, Chou Janet. Autoimmunity and Immunodeficiency. Curr Opin Rheumatol. 2020,32:168-74.

10. Barmettler S, Price C. Continuing IgG replacement therapy for hypogammaglobulinemia after rituximab–for how long? J Allergy Clin Immunol. 2015;136(5):1407-9.

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