Thyroid Research

CASE REPORT

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Successful outcome of Rituximab treatment based on lymphocyte immunophenotyping in active Thyroid Eye Disease: a case report

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Abstract

Background Rituximab, an anti-CD20 monoclonal antibody that depletes B-cells, is a potential second-line treatment for moderate-to-severe active Thyroid Eye Disease that is resistant to steroids. This report comprehensively analyzes the influence of rituximab on the immune system of a patient, detailing immunophenotyping of blood, thyroid, and cervical lymph nodes before and after therapy.

Case presentation A 53-year-old male presented with Thyroid Eye Disease reactivation 18 months after previous treatment with intravenous methylprednisolone, and it was successfully treated with two 500 mg intravenous doses of rituximab, achieving disease inactivation. The effects of rituximab were monitored on paired blood-, thyroid- and cervical lymph nodes-derived lymphocytes by repeated ultrasound-guided fine-needle aspiration. Only after two rituximab doses Thyroid Eye Disease inactivated, when B cells were markedly reduced in lymph nodes with depletion of germinal B cells. Follicular T cell subsets and T-cell activation markers were also affected, probably due to the lack of B-cell support. Twenty-two weeks after inactivation, the patient underwent decompression surgery of the right eye due to residual proptosis. The immunophenotyping of retro-orbital tissue showed persistence of B cells, with different subsets compared with other depots.

Conclusion This is the first report of personalized therapy in active Thyroid Eye Disease based on monitoring tissue-resident lymphocytes. Such novel approach could lead to more targeted and effective treatments in the future.

Keywords Thyroid eye disease, Rituximab, Lymphocyte immunophenotyping, Graves' basedow disease

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Background

Thyroid eye disease (TED) is the commonest extrathyroidal manifestation of Graves' disease (GD), a condition of autoimmune hyperthyroidism due to the development of autoantibodies stimulating the thyrotropin receptor (TRAb) [1, 2]. TED is an inflammatory autoimmune-mediated disorder of the orbital tissues, characterized by local immune infiltration, adipose tissue expansion, fibroblasts proliferation and excessive production of glycosaminoglycans, usually associated with early inflammation (active disease) defined by Clinical Activity Score (CAS) ≥ 3/7 or ≥ 4/10, and subsequent inactive fibrotic phase with CAS < 3/7 or < 4/10 [3]. CAS is based on seven signs: spontaneous retrobulbar pain, gaze evoked pain, eyelid erythema, eyelid edema, conjunctival hyperaemia, chemosis, and inflammation of the caruncle. For follow-up, the score extends to ten points, adding an increase in exophthalmos, a decrease in eye movements, and a decrease in visual acuity to monitor disease progression. To assess disease severity, ophthalmological evaluations include: palpebral aperture (vertical palpebral fissure width), diplopia (graded as absent, intermittent, inconstant or constant), and proptosis (anterior globe protrusion measured by Hertel exophthalmometer) [3]. Immunosuppressive medical interventions are the cornerstone of therapy during the active inflammatory phase, and intravenous methylprednisolone (ivMP) remains a common initial treatment option. However, for patients with chronic, inactive disease where fibrotic changes have occurred, surgical correction is necessary to address the lasting functional and cosmetic deficits, including proptosis, persistent diplopia, and significant lid retraction. Rituximab (RTX), an anti-CD20 monoclonal antibody, is a second-line therapy for active moderate-to-severe TED, when ivMP fails [4]. RTX depletes CD20-expressing B cells, including most naïve and memory B cells but not plasma cells or early progenitors [5]. The exact mechanism of RTX's efficacy in autoimmune disease is still unclear; however it has emerged as a multifaceted agent with significant implications for both B and T cell dynamics. This study provides immunophenotyping of paired blood and tissue-resident lymphocytes before, during, and after RTX in a clinical case of relapsed TED after ivMP, to explore RTX's immunological mechanisms. Lymphocytes were obtained from blood, thyroid, and neck lymph nodes (LN) via ultrasound-guided fine needle aspiration (US-FNA) at baseline (week 0) and 4, 13, 21 and 37 weeks after RTX, and they were immunophenotyped by flow cytometry (FACSymphony TM cytometer; Becton Dickinson) for markers CD45, CD25, CXCR5, PD1, CD38, BCL6 (BD Biosciences), CD3, CD4, CD19, IL-7R (BD Horizon), CD27, IgD (Biolegend) and Live/Dead-Aqua (ThermoFisher). CD69 (BD Horizon) and CD40L (Biolegend) activation markers were detected after stimulating lymphocytes with phorbol 12-myristate 13-acetate and ionomycin (Sigma Aldrich). After TED inactivation, the patient underwent decompression surgery as part of his rehabilitation surgery and lymphocytes were isolated from orbital fat by mechanical and enzymatic degradation (Human Tissue Dissociation Kit, Miltenyi Biotec) and immunophenotyped. Throughout this period, during which the patient was followed, serum TRAb concentrations were measured by Immulite 2000/2000 XPi TSI (Siemens, Erlangen, Germany) and Stimulating TRAb (TSAb) were assessed by in-house luciferase bioassay [6] and expressed as SI.

Case presentation

A 53-year-old male ex-smoker was referred to our clinic for a sudden progression of active TED. He presented with a CAS of 3/7, characterized by eyelid swelling, eyelid hyperaemia, and chemosis. Clinical examination revealed a proptosis of 29/22 mm (Right Eye (RE)/Left Eye (LE)), palpebral aperture of 12/9 mm respectively in right and left eye, and intermittent diplopia. Retrospectively, his TED had been diagnosed five years prior in a mild, inactive form (CAS 0/7, RE/LE proptosis 22/21 mm, palpebral aperture RE/LE 11/8 mm). This was 26 years after his initial diagnosis of GD, which was treated with radioiodine ablation after a four-year course of methimazole. He had been stable on levothyroxine for the subsequent 22 years. For his active TED the patient received a total of 4.5 g ivMP in 12 weekly infusions, with resolution of inflammation but worsening of proptosis (RE/LE 33/23 mm) and ductions (CAS 2/10), palpebral aperture RE/LE 16/11 mm and evolution to constant diplopia.

Eighteen months after ivMP (Week 0), at age 55, TED reactivated in the LE only: eyelid swelling, eyelid hyperaemia, caruncle inflammation, proptosis worsening RE/LE 31/29 mm and ductions (CAS 5/10), constant diplopia and palpebral aperture RE/LE 19/11 mm. Patient was euthyroid on levothyroxine with TSH 1.1 mIU/L (reference range, 0.28–4.3 mIU/L), TRAb 1.87 KIU/L (reference range, 0-0.55 KIU/L) and positive TSAb with thyroid stimulating activity (SI) of 1.89 (reference range, 0-1.5).

As shown in Fig. 1, after TED reactivation the patient, who weighed 80 kg, was treated with 500 mg RTX intravenously (Week 0). Four weeks later his TED was still active in the LE (CAS 6/10: eyelid hyperemia, eyelid swelling, caruncle inflammation, conjunctival hyperemia, chemosis, and worsening of ductions), with proptosis RE/LE 31/29.5 mm and palpebral aperture RE/LE 20/10 mm. Immunophenotyping showed complete B-cell depletion in both blood and thyroid, whereas LN-resident B cells were only decreased compared to baseline (-65%), with relative increase of switched memory B cells (SwME; CD19 + CD27 + IgD-) and double

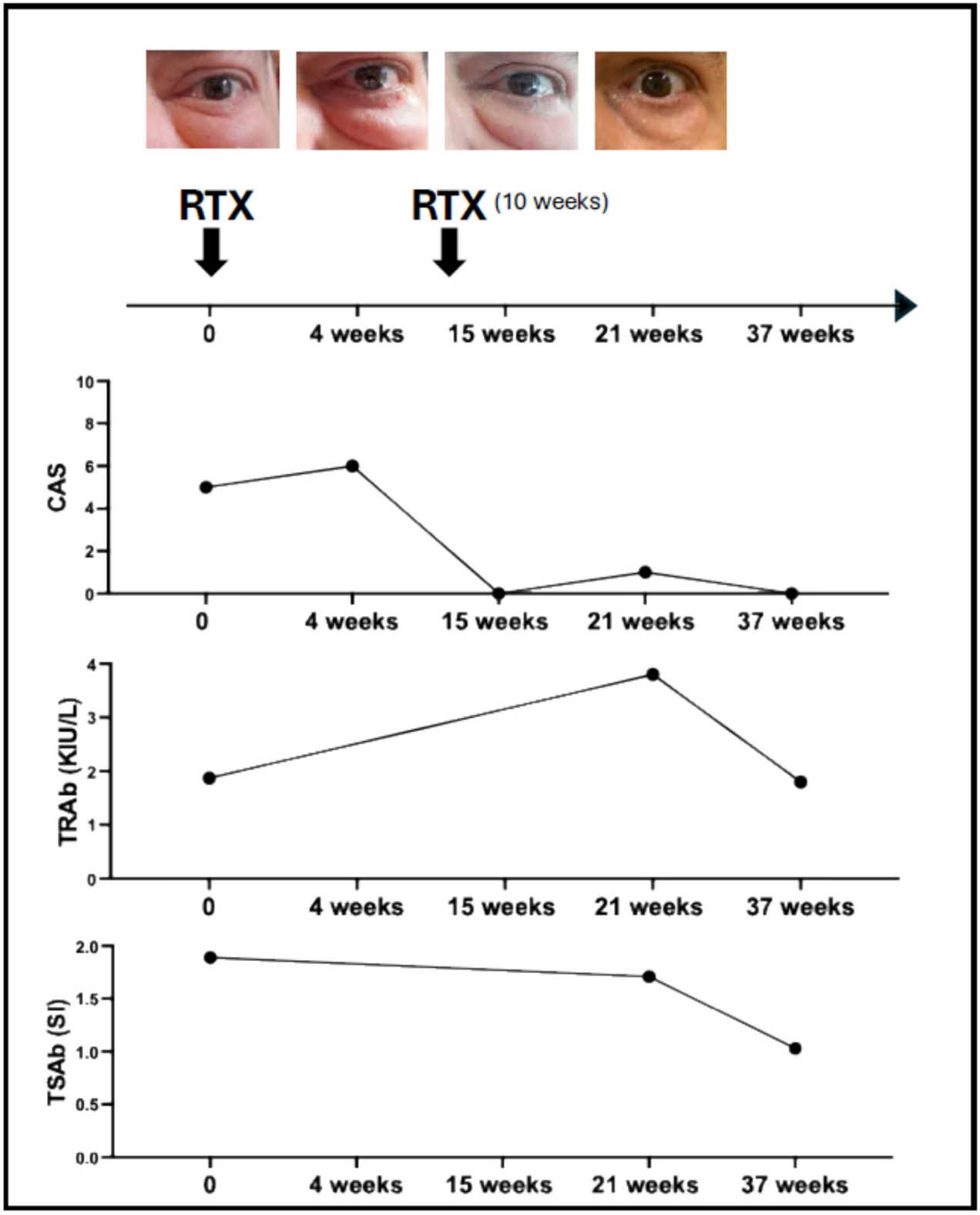

Fig. 1 Timeline representing the patient's clinical history, clinical activity score (CAS), serum concentration (KIU/L) of autoantibodies against thyrotropin receptor (TRAb), and the stimulation index (SI) of autoantibodies stimulating the thyrotropin receptor (TSAb), before, during and after rituximab (RTX) therapy to the end of follow-up

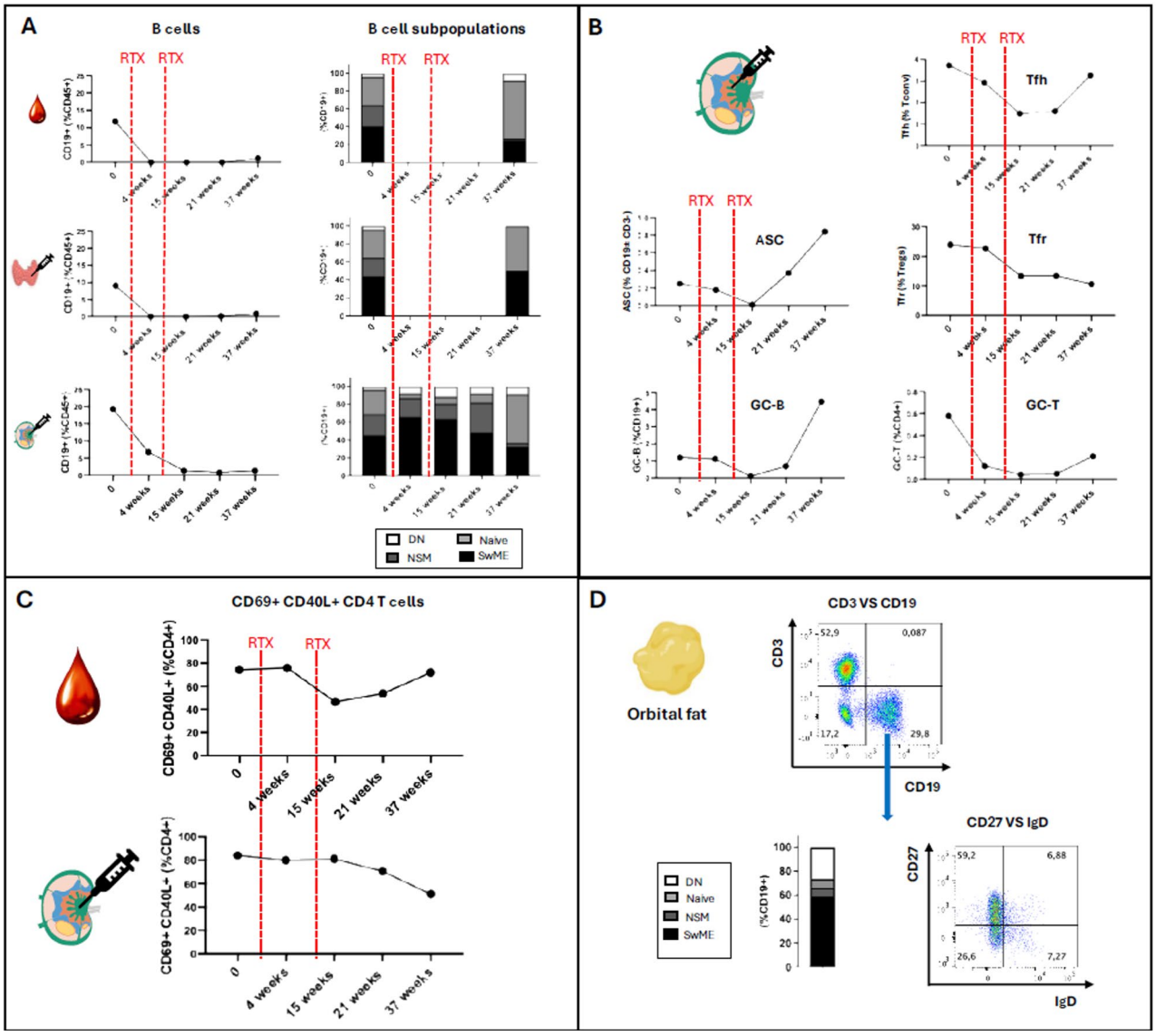

Fig. 2 Analysis of blood, thyroid and lymph node (LN)-derived lymphocytes at several time-points before, during and after treatment with rituximab (RTX). The graphs show the weeks starting from the first dose of RTX. **A**: Percentage of B cells (CD19 + CD3-) among total CD45 + lymphocytes and, in the bar graph, percentage of B cell subsets among total CD19 + lymphocytes (switched memory B (SwME; CD27 + IgD-), non-switched memory B (NSM; CD27 + IgD+), naïve (CD27-IgD+) and double-negative (DN; CD27-IgD-) B cells) in patient's blood, thyroid and LN. **B**: Percentage of GC-B cells (CXCR5 + BCL6+) among total CD19 + cells; and percentage of antibody secreting cells (ASC; CD27hiCD38hi) among total CD19 ± CD3- cells in patient's LN. Percentage of T follicular helper (Tfh; CXCR5 + PD1 + IL7R ± CD25-) among T conventional (Tconv; CD4 + IL7R ± CD25-) cells, T follicular regulatory (Tfr; CXCR5 + PD1 + IL7R low/- CD25+) among T regulatory (Treg; CD4 + IL7R low/- CD25+) cells and germinal centre T (GC-T) cells among total CD4 + T cells. **C**: Percentage of CD69 + CD40L + T cells among total CD4 + T cells in patient's blood and LN. **D**: Representative dot plots showing the expression of CD3 versus CD19 in CD45 + cells and the expression of CD27 versus IgD in CD19 + B cells of orbital fat obtained 37 weeks after the first RTX dose. The bar graph shows the percentage of B cell subsets: SwME, NSM, naïve and DN infiltrating the orbit

negative (DN; CD19 + CD27-IGD-) B cells, along with relative decrease of naïve B cells (CD19 + CD27-IgD+), and unchanged frequencies of non-switched B cells (NSM; CD19 + CD27 + IGD+; Fig. 2A). Antibody secreting cells (ASC; CD27hiCD38hiCD19 ± CD3-) and germinal centre B cells (GC-B; CXCR5 + BCL6 + CD19+) were not affected by therapy within LNs (Fig. 2B). Similarly, no differences were detected in the proportion of T follicular regulatory (Tfr; CXCR5 + PD1 + CD127lo/-CD25+) on total T regulatory (Treg; IL7Rlow/-CD25+) cells in blood, thyroid (data not shown) and LNs, whereas the frequencies of T follicular helper (Tfh; CXCR5 + PD1 + CD127 ± CD25-) on total T conventional (Tconv; IL7R+/-CD25-) cells and germinal centre T cells (GC-T; CXCR5hiPD1hi) cells on total CD4 + T cells were

slightly and markedly decreased compared to baseline, respectively (Fig. 2B).

Ten weeks after the first RTX infusion his TED was persistently active, and a second 500 mg RTX dose was given. After further five weeks (week 15 after first RTX infusion) his TED achieved inactivation (CAS 0/10), and remained inactive also at weeks 21 and 37, with stable proptosis RE/LE 31.5/29.5 mm, palpebral aperture RE/LE 18/10 mm and constant diplopia. At 15 weeks B cells were not detectable in both blood and thyroid, while were markedly reduced within LNs (-93%; Fig. 2A), also showing depletion of both GC-B cells and ASC (Fig. 2B). Consistently, LN-resident Tfh, Tfr and GC-T cells showed a marked decrease (Fig. 2B), along with reduced expression of T cell activation markers CD69 and CD40L in blood (Fig. 2C).

At 21 weeks a slight increase in TRAb levels (3.8 KIU/L) was noted, while TSAb (SI 1.71) did not change. At this time, B cells were absent or reduced across all three compartments (Fig. 2A). Within LNs GC-B cells and ASC began to repopulate, whereas Tfh, Tfr and GC-T cells remained low (Fig. 2B). CD69 and CD40L expression started to decrease within LNs but showed initial recovery in blood (Fig. 2C).

By 37 weeks after therapy, all compartments showed initial total B cells repopulation. Within LNs naïve B cells markedly increased, whereas both SwME and NSM memory B cells were slightly reduced (Fig. 2A). GC-B cells and ASC continued to increase above baseline level, together with initial Tfh and GC-T cells repopulation (Fig. 2B). CD69 and CD40L expression continued to recover in blood, and to decrease in LN (Fig. 2C).

No differences were observed in CD3 + T cells frequency among total CD45 + lymphocytes before and after RTX therapy, as well as throughout the follow-up period in all three compartments: blood, thyroid and LNs (data not shown).

At 37 weeks TRAb levels had decreased to 1.8 KIU/L with negative TSAb (SI 1.03), and the patient underwent right orbit medial, lateral, and inferior wall decompression surgery for his predominantly right exophthalmos. Orbital immunophenotyping revealed the presence of CD3+ (53% of CD45+) and CD19+ (30% of CD45+) lymphocytes, primarily SwME and DN B cells, with only a small fraction of NSM and naïve B cells (Fig. 2D). Tfh and Tfr cells constituted 12.2% and 9.45% of total Tconv and Treg cells, respectively. No ASC, GC-B, or GC-T cells were detected (data not shown).

Following decompression surgery, exophthalmos was substantially symmetrical in both eyes. Therefore, at patient's request LE decompression was deferred and strabismus surgery was later performed. Despite sustained B-cell depletion following RTX treatment and during follow-up, the patient experienced no major infections or adverse effects.

Discussion and conclusions

We report a case of successful RTX therapy in a TED patient, where clinical efficacy was achieved after two doses (15 weeks), a timeframe consistent with previous studies [7, 8]. This is the first report to detail these effects through paired immunophenotyping of blood, thyroid, and cervical lymph nodes (LN) conducted before, during, and after treatment. RTX rapidly depletes peripheral B cells for up to six months, depending on the dose employed, followed by slow repopulation [9–11], however little is known about its effect on tissue-resident lymphocytes. B-cell depletion in organ specific autoimmune disease was shown after RTX in patients with systemic lupus erythematosus (appendix) [12], immune thrombocytopenic purpura (spleen) [13], Sjögren syndrome (salivary glands) [14], and TED (thyroid) [11, 15]. In this report a single 500 mg RTX dose was shown to deplete B cells in blood and thyroid gland, while within neck LNs a significant B-cell reduction occurred only after a second RTX dose, when TED inactivation was also achieved. LN-resident B cells in rheumatoid arthritis patients were incompletely depleted four weeks post-first RTX 1000 mg dose and two weeks post-second 1000 mg dose, consistent with prior studies [16]. Additionally in rheumatoid arthritis patients post-RTX B-cell reduction, but not complete depletion, was reported after three months in bone marrow aspirates [17], and one-to-four months in synovial samples [18]. These results suggest that a single RTX dose may not fully deplete B cells in all target tissues, suggesting that clinical efficacy may relate to the dose administered.

RTX efficacy relies on depleting B cell subpopulations, except precursors and plasma cells [19]. The study of LN infiltrates allowed monitoring of B cell subsets over time, which was not possible in blood and thyroid, totally depleted after the first dose of RTX. Naïve B cells were rapidly depleted after four weeks following RTX therapy, as also observed in other autoimmune diseases [16]. Interestingly, these cells later exhibited rapid repopulation and became the predominant B cell subtype at 37 weeks of follow-up (Fig. 2A). LN-resident GC-B cells were depleted only after the second RTX dose. The transient depletion of ASC, which do not express the CD20 antigen and occurred only after the second dose, was not caused by RTX. Instead, it is a likely consequence of their precursors' depletion within GCs. These findings align with previous observations showing that LN-resident plasma cells remained unaffected in rheumatoid arthritis patients after RTX treatment [16]. However, Thurlings et al. observed a marked reduction in the synovial of patients with rheumatoid arthritis responders to RTX

therapy, but not in non-responders, confirming the presence of indirect effects on short-lived plasma cells [18]. Finally in our study both GC-B cells and ASCs rapidly repopulated within LNs at 21 weeks after RTX, in line with naïve B cells increase and memory B cells relative reduction; these findings were confirmed at 37 weeks after RTX.

B cells may act as antigen-presenting cells and co-stimulate T-cells, and this may explain why RTX is effective in T-cell-mediated diseases like TED [20, 21]. In this patient no changes were observed in the frequency of total T cells after RTX treatment, consistently with previous findings in moderate-to-severe TED [7]. However, a reduction of LN-resident Tf and GC-T cell subsets was observed after two RTX doses, as well as the decreased expression of T cell early activation markers CD40L and CD69. These findings are consistent with other studies in autoimmune diseases [22–24] and suggest that RTX-induced B-cell depletion may disrupt GC activity by affecting the B cell function of antigen presentation. The effect of RTX on TRAb concentrations is still conflicting and debated in literature, due to differences in disease stage, individual immune responses, and the persistence of ASCs, not directly affected by RTX [19]. In our study, serum TRAb concentrations were slightly above normal and did not decrease in relation to B cell depletion. Both TRAb and TSAb showed a slight reduction 37 weeks post-treatment, in contrast to existing data showing a selective effect of RTX on TSAb only, without affecting binding TRAb [25]. Further studies on a higher number of patients are needed to clarify RTX effects on TRAb concentrations and subtypes with different biological activity.

Of interest is the immunophenotyping of retro-orbital tissue after RTX treatment, which revealed a marked presence of T and B lymphocytes, with predominant SwME and DN, and only few NSM and naïve B cells, differently from what observed in blood, thyroid and LN, where naïve B cells represented the predominant population. Similar results were reported by Nielsen et al. [25], who observed that orbital tissues from TED patients six months after RTX treatment had B cell counts comparable to those of normal orbital tissues. In contrast, Chong et al. [26] and Salvi et al. [11] demonstrated a complete orbital B- and T-cell depletion 7 days and 9 months post-RTX, respectively. It remains unclear in this patient to which extent orbital B lymphocytes were affected by RTX treatment, or if they repopulated earlier, before orbital surgery was performed.

In conclusion RTX immunotherapy for TED was confirmed to be effective and safe in this patient unresponsive to steroid therapy. This study offers new insights into the immune-modulating effects of RTX, specifically highlighting its impact on both B and T cells and GC in organ specific compartments of autoimmune thyroid disease. The accessibility via US-FNA of lymphocytes from tissues targeted by immune reactions provides unique insights into the effects of treatments, useful to develop precision and personalized therapy approaches.

Abbreviations

TED	Thyroid eye disease
GD	Graves' disease
TRAb	Antibodies stimulating the thyrotropin receptor
CAS	Clinical Activity Score
ivMP	Intravenous methylprednisolone
RTX	Rituximab
US-FNA	Ultrasound-guided fine needle aspiration
TSAb	Stimulating TRAb
LN	Neck lymph nodes
RE	Right Eye
LE	Left Eye
SwME	Switched memory B cells
DN	Double negative
NSM	Non-switched B cells
ASC	Antibody secreting cells
GC-B	Germinal centre B cells
Tfr	T follicular regulatory
Treg	Total T regulatory
Tfh	T follicular helper
Tconv	Total T conventional
GC-T	Germinal centre T cells

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Author contributions
All authors made individual contributions to authorship. M.A., C.R., N.C., M.S. and I.M. were involved in the diagnosis and management of the patient. S.M. and G.M. were involved in immunophenotyping analysis. N.C., M.S. and I.M. were responsible for patient's treatments. M.A., S.M., M.S. and I.M. were involved in manuscript preparation. All authors reviewed and approved the final draft.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the ethical committee of Milano Area 2 (permission 0004946 69_2020bis 7/2/2020 ID 1333).

Consent for publication
Written informed consent was obtained from the patient for the publication of this case report.

Competing interests
I.M. is an Associate Editor of the Journal and the Guest Editor of this Collection; she was not involved in handling this manuscript during the manuscript review process. She received consulting fees from Alexion Pharma, Amgen, Merck, Tourmaline, Argenx and Lundbeck. M.S. received consulting fees from IBSA, Argenx, Third Rock Ventures, Tourmaline, Immunovant, Lycia, Amgen, Viridian, Merck. M.A., S.M., C.R., G.M., N.C. have no disclosures to declare.

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