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Case Report

Rituximab for a rare pediatric case of concurrent thyroid eye disease and myasthenia gravis

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***Abstract*:** Rituximab (RTX) is a humanized chimeric anti-CD20 monoclonal antibody that leads to immunosuppression through rapid depletion of B lymphocytes. It has been demonstrated to be useful in treating both thyroid eye disease (TED) and myasthenia gravis (MG), respectively. However, the effectiveness of RTX in concurrent TED and MG cases is unclear and not previously reported in the literature. In this study, we describe a 13-year-old girl who presented with a 10-year history of general MG and a 1-year history of Graves' disease, bilateral proptosis, eye motility restriction, and lagophthalmos. A comprehensive evaluation confirmed the diagnosis of concurrent TED and MG. Satisfactory effectiveness was observed after RTX treatment without side effects. Based on the described observations, we suggest that RTX should be further explored as a treatment option for patients with concurrent TED and MG.

Plain language summary

Rituximab to treat thyroid eye disease compounded with myasthenia gravis in a child

Selecting the appropriate medication for the simultaneous management of rare conditions like concurrent thyroid eye disease (TED) and myasthenia gravis (MG) presents a challenge, as there is no one-size-fits-all approach. This study describes the case of a 13-year-old girl with this rare condition, who was not willing to accept steroid treatment because of its side effect. Therefore, we decided to use rituximab (RTX), a monoclonal antibody that works by targeting immune cells, with the hypothesis that it could address both conditions concurrently. The treatment worked remarkably well that both conditions improved without obvious adverse effects. This marks the first instance where RTX has been demonstrated to manage TED and MG simultaneously and effectively. Our findings suggest that RTX could represent a pivotal treatment strategy, potentially providing a more comprehensive and effective approach to care for individuals facing concurrent TED and MG, rather than separate treatments for each disease.

Keywords: thyroid eye disease, myasthenia gravis, pediatrics, rituximab

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Background

Autoimmune thyroid disorders, particularly Graves' disease, are the most common co-occurring autoimmune conditions in myasthenia gravis (MG).[1–3] As the main extrathyroidal manifestation of Graves' disease, thyroid eye disease (TED) can

be confounded when it coexists with MG, complicating the diagnosis.[4,5] Furthermore, Graves' disease and MG share a see-saw relationship where treating one condition may exacerbate the other.[6] This phenomenon extends to the treatment of concurrent TED and MG. Therefore, identifying concurrent TED and MG precisely as well as selecting appropriate and efficacious treatment strategies can be both critical and challenging.

Common polypharmacy strategy includes pyridostigmine combined with either anti-thyroid drug, glucocorticoids, or immunosuppressants.[2,7,8] However, it increases the risk of drug interactions and side effects, thus monoclonal antibody therapy targeting a common pathway for both diseases may provide a novel approach. Rituximab (RTX) is a humanized chimeric anti-CD20 monoclonal antibody that leads to immunosuppression through rapid depletion of B lymphocytes.[9] Previous studies revealed that RTX may reduce autoreactive T cells that are involved in the pathogenesis of TED by directly targeting B cells in their antigen-presenting cell function.[10] Meanwhile, RTX can effectively target the pathogenic autoimmune B cells involved in MG, reducing autoantibody production and achieving therapeutic benefits.[7] Though the mechanism of RTX in treating TED or MG is not fully illustrated, RTX holds promise for the simultaneous treatment of concurrent TED and MG without the see-saw effect. However, its efficacy in the comorbidity remains uncertain.

This report details the case of a 13-year-old girl with concurrent TED and MG treated with RTX, offering insights into its potential as a treatment option and contributing to the limited knowledge of managing such complex cases.

Case presentation

A 13-year-old girl presented with a 1-year history of Graves' disease, bilateral proptosis, eye motility restriction, and lagophthalmos. Her hyperthyroidism was adequately managed with methimazole. In addition, she was documented to have a 10-year history of general MG with episodic bilateral upper eyelid ptosis and systemic fatigue, which was controlled by pyridostigmine bromide and prednisone intermittently. Physical examination showed proptosis (23 mm OD, 26 mm OS), increased palpebral fissure width (10 mm OD, 9 mm OS), and ptosis OS. Lifting the ptotic eyelid did not improve contralateral retraction, confirming her true eyelid retraction instead of pseudoretraction. In addition, the patient exhibited bilateral redness and swelling of the caruncle and conjunctiva, severe eyelid swelling, and a bilateral clinical activity score (CAS) of 4. She experienced severe bilateral eye motility restriction in all directions and diplopia when abducted to the right (Figure 1(a)). Her thyroid function had returned to normal, yet the level of thyrotropin receptor antibodies (TRAb: 9.12 IU/L) remained significantly elevated. She was seropositive for anti-acetylcholine receptor antibodies (0.59 mmol/L). A neostigmine test and the repetitive nerve stimulation (RNS) test of her orbicularis oculi muscle and left abductor pollicis brevis muscle were also positive. A forced duction test showed the extraocular muscle dysfunction to be paretic, and thus primarily due to MG. Orbital magnetic resonance imaging (MRI) revealed slightly thickened bilateral extraocular muscle bellies and abnormally increased signal intensity on T2-weighted imaging (Figure 1(b) and (c)). Considering the above clinical presentation and examination results, this patient was diagnosed with coexisting TED and general MG.[11,12]

She had previously experienced significant weight gain and a decline in quality of life while on oral glucocorticoids for TED, which had exhibited only limited effectiveness. Thus, she and her guardians were seeking treatment options that did not include glucocorticoids. Orbital radiotherapy is not recommended for children. Teprotumumab was not available yet in this region. Though Eculizumab is useful in the treatment of MG, no evidence supports its efficacy in treating TED. Following a comprehensive discussion by a multidisciplinary team, the recommendation was made to treat the patient with RTX (at an intravenous dosage of 375 mg/m^2, biweekly for a total of two doses) and informed consent of the patient and her guardians was secured.

The patient underwent three follow-up visits at 3, 6, and 12 months after RTX treatment, respectively. Peripheral CD20$^+$ B cells depleted to zero at the 3-month follow-up, which returned to normal levels by the 6-month follow-up. She experienced a significant improvement in eye movement and complete resolution of diplopia (Figure 2(a)). Furthermore, her proptosis improved to 21 mm OD, 23 mm OS 12 months after RTX treatment. The asymmetry in eyelid positioning was also alleviated. The CAS improved to 2 for both eyes.

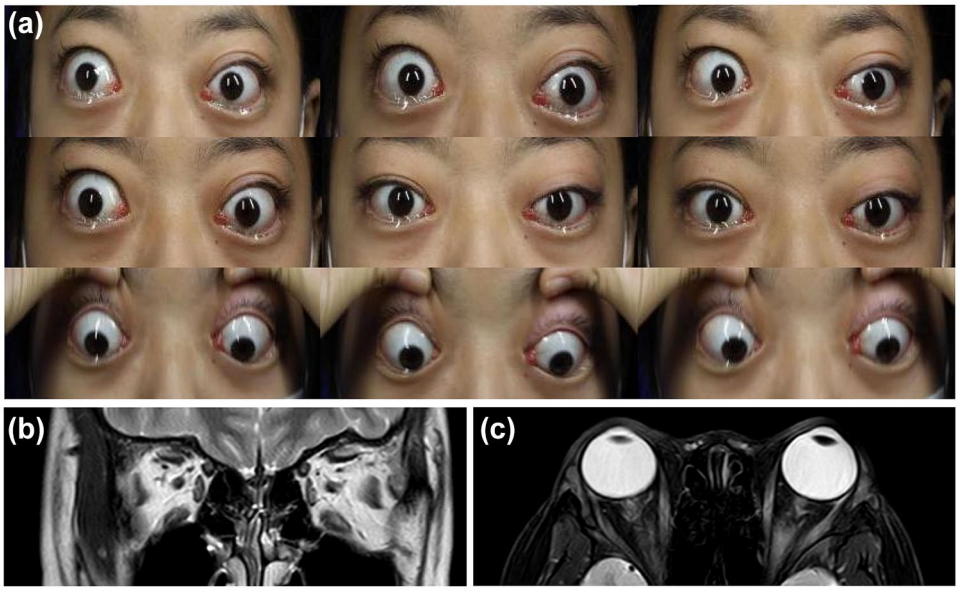

Figure 1. Nine-directional ocular photographs and orbital MRI before treatment. (a) The nine-directional ocular photographs revealed pronounced proptosis and bilateral restricted eye motility of inward, outward, and upward. (b, c) Orbital MRI revealed thickening extraocular muscles and abnormally increased signal intensity of extraocular muscles on coronal (b) and transverse (c) T2-weighted imaging.
MRI, magnetic resonance imaging.

In addition, the ptosis, lagophthalmos, photophobia, tearing and pain, and overall fatigue were significantly relieved. During the treatment, levels of TRAb decreased to normal levels. The orbital MRI indicated an improvement in orbital inflammation (Figure 2(b) and (c)). Moreover, she experienced no side effects from RTX and noted a significant enhancement in her quality of life, especially regarding visual function. After 12 months of RTX treatment, she underwent orbital decompression surgery to further enhance her appearance, which proved to be remarkably effective. The initial and follow-up serological data are presented in Table 1.

Discussion

The co-occurrence of TED and MG is rare. Specifically, TED manifests in approximately 1.3% of MG cases, while MG presents in 0.7%–1.3% of individuals with TED.[1,13] Furthermore, few cases of concurrent TED and MG have been reported in the pediatric population.[14] The pathogenesis of concurrent TED and MG is likely multifactorial and has been inadequately elucidated. However, the co-occurrence of MG and TED may be attributable a shared genetic background as well as possible immunological cross-reactivity against common autoimmune targets in the extraocular muscle.[15]

The hallmark diurnal fluctuation of OMG symptoms and the distinct external ocular manifestations of TED generally allow for clear differentiation between the two conditions.[2] However, due to some overlapping ocular symptoms, diagnosing TED and MG in the same individual can still be challenging, requiring careful clinical and diagnostic evaluation.[2] It is important to understand that in patients with concurrent TED and MG, symptoms of upper eyelid retraction and ptosis may counteract each other.[16,17] Hering's law and pseudoretraction can influence eyelid position assessment in MG, potentially leading to misinterpretation.[18] In addition, the interpretation of RNS results in these patients requires careful consideration, as the observed decrement may not solely indicate MG-related muscle weakness but could also be attributed to TED. Specifically, there are two possible scenarios: first, thyrotoxicosis itself can lead to RNS abnormalities, and second, prolonged lagophthalmos caused by TED may also result in RNS decrement.[19] Furthermore, although both TED and MG can lead to limited eye movement, in this particular case, the lack of both prominent thickening

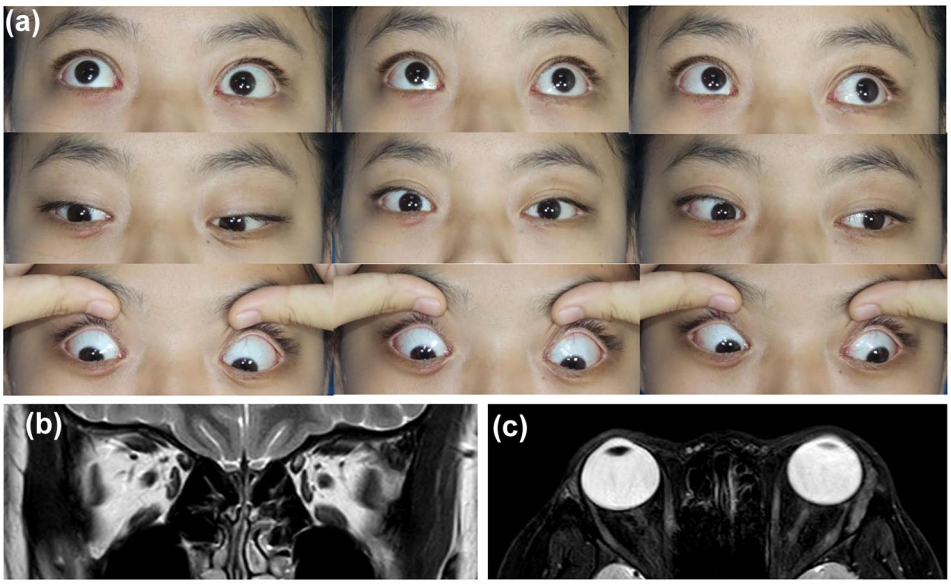

Figure 2. Nine-directional ocular photographs and orbital MRI after RTX treatment and orbital decompression surgery. (a) The nine-directional ocular photographs revealed significant ocular improvement after the surgery. (b, c) Orbital MRI demonstrated improvement of orbital inflammation on coronal (b) and transverse (c) T2-weighted imaging.
MRI, magnetic resonance imaging; RTX, rituximab.

Table 1. Changes in thyroid function and autoantibodies result from the beginning to the last follow-up.

Stage \ Item	TSH (μIU/mL)	FT3 (pg/mL)	FT4 (ng/dL)	TGAb (IU/mL)	TPOAb (IU/mL)	TRAb (IU/L)	TG (ng/mL)
Before treatment	1.04	3.36	0.80	18.90	45.80 ↑	9.12 ↑	31.74
3 months after RTX	1.89	3.21	0.74	14.00	26.20 ↑	2.96 ↑	114.82
6 months after RTX	0.91	3.36	0.80	12.40	12.60 ↑	0.85	71.90
12 months after RTX	1.85	2.34	1.29	21.08	52.87 ↑	1.22	128.60 ↑

"↑" indicates levels above the normal range; "↓" indicates levels below the normal range, and the absence of a symbol indicates values within the normal range.
FT3, free triiodothyronine; FT4, free thyroxine; RTX, rituximab; TG, thyroglobulin; TGAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; TRAb, thyroid receptor antibodies; TSH, thyroid stimulating hormone.

of the extraocular muscles and increased signal intensity on T2-weighted imaging is inconsistent with the severity of the patient's symptoms.[1,20] Therefore, under the masking effect of such confounding symptoms, the results of imaging studies may be difficult for clinicians to interpret. In such a case, a forced duction test is needed to determine whether the myopathy is paretic (as in MG) or restrictive (as in TED). In total, a comprehensive evaluation, including clinical symptoms, serological evidence, and neurological examination (e.g., Cogan's lid twitch test), is essential to accurately differentiate between these possibilities and guide appropriate management. In this case, we confirmed the diagnosis of concurrent TED and MG after acquiring corroborative evidence from laboratory and imaging tests, as well as a forced duction test and careful analysis of ocular manifestations.

Although the detection of concurrent TED and MG has been discussed previously, an appropriate

and efficacious treatment strategy for this condition remains unclear.[1] The patient's significantly limited eye movement, causing diplopia and poor vision, reflects the confounding symptoms of TED and MG. However, the forced duction test showed the extraocular muscle dysfunction to be paretic, and thus primarily due to the MG. Moreover, given that addressing either eyelid retraction or ptosis could potentially aggravate the other, ensuring the maintenance of normal eyelid positioning also requires a comprehensive strategy that simultaneously tackles both issues.[7] RTX provided a novel approach in this particular case.

Given the autoimmune nature of both TED and MG, characterized by increased autoantibodies, the efficacy of RTX has been studied in both conditions.[21–23] The two randomized controlled trials performed to determine the efficacy of RTX in TED reached conflicting conclusions, likely related to the shorter disease duration of the patients in the trial that showed more beneficial effects.[22,24,25] It is currently considered a second-line treatment for patients with moderate-to-severe and active TED of short duration, refractory to intravenous glucocorticoids.[11] RTX has been reported to be effective in treating MG, especially in a subset of patients with MuSK MG, and serves as an option if patients fail or do not tolerate other immunosuppression agents.[21,26–28] It is also noteworthy that RTX is considered to be relatively safe, with mild infusion-related reactions being the most commonly reported adverse event.[29] Using RTX in pediatric patients with either disease may reduce the adverse effects of broad-spectrum medications like glucocorticoids and cholinesterase inhibitors. To our knowledge, this is the first report on the effectiveness of RTX treatment in a patient with concurrent TED and MG, although the efficacy of RTX has been previously documented in each disease individually. However, despite the diagnosis of concurrent TED and MG, the patients diplopia was shown by the forced duction test to be mostly paretic and thus primarily due to the MG. Thus, one can speculate that the beneficial effect of the RTX on the extraocular dysfunction was primarily on the MG component of the disease.

Given the mechanistic similarities between RTX and FcRn-targeting therapies—both aim to reduce pathogenic antibodies, albeit through different pathways (RTX via B-cell depletion and FcRn inhibitors via IgG degradation)—it is reasonable to hypothesize that FcRn inhibitors may also have therapeutic potential in treating concurrent TED and MG.[30] A notable example is the use of efgartigimod, which has been shown to treat both MG and other autoimmune disorders, such as stiff-person syndrome, simultaneously.[31] Furthermore, clinical trials (NCT06307613) are evaluating its potential for TED, while another FcRn inhibitor, batoclimab, has already shown promising results in TED.[32] These findings suggest that FcRn inhibitors could represent a viable alternative for managing TED-MG comorbidity. In summary, utilizing a single monoclonal antibody therapy to simultaneously treat TED-MG comorbidity could represent a practical and well-tolerated therapeutic approach.

Conclusion

Concurrent TED and MG in pediatric patients are rare but have been previously reported. A thorough evaluation that includes clinical, hematological, imaging, and specialized tests is recommended for accurate diagnosis and clinical management. This case highlights the favorable therapeutic efficacy of RTX with minimal side effects in a patient with both conditions, suggesting that it may represent a prudent and well-tolerated treatment approach in such scenarios.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient and her guardians provided written informed consent for publishing these data in the report.

Author contributions

Haiyang Zhang: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Ting Lu: Formal analysis; Visualization; Writing – original draft; Writing – review & editing.

Yinwei Li: Investigation; Resources; Writing – review & editing.

Haixia Guan: Validation; Writing – review & editing.

Rebecca S. Bahn: Validation; Writing – review & editing.

Huifang Zhou: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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