New onset or deterioration of thyroid eye disease after mRNA SARS-CoV-2 vaccines :report of 2 cases and literature review

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Abstract (247/250)

Context

Occurrence of Graves' disease (GD) has been reported following SARS-CoV-2 vaccine administration, but little is known about thyroid eye disease (TED) after SARS-CoV-2 vaccination.

Methods

We report two cases of TED activation following SARS-CoV-2 vaccination: one case of TED worsening in a patient with GD, and one of de novo active TED progressing to dysthyroid optic neuropathy in a patient with a history of Hashimoto's hypothyroidism. Our literature search revealed 8 additional reported TED cases associated with SARS-CoV-2 vaccination until June 2022. We review the characteristics, duration and management of TED following SARS-CoV-2 vaccination in these cases.

Results

Of all 10 reported TED cases following SARS-CoV-2 vaccination, four cases developed new onset TED and 6 cases with prior stable TED experienced significant deterioration. Six patients had known Graves' disease and 2 patients had Hashimoto's thyroiditis. Two cases progressed to dysthyroid optic neuropathy, 6 had moderate/severe active disease and 2 cases had mild disease that did not require treatment. Seven TED cases received teprotumumab and had a favorable response, two of which had prior limited response to initial prednisone or methylprednisolone and tocilizumab therapy.

Conclusions

New diagnosis or deterioration of TED after mRNA SARS-CoV-2 vaccination can occur, with most cases described in patients with underlying autoimmune thyroid disease. Our report raises awareness to this potential complication to promote early recognition and prompt management of TED associated with mRNA SARS-CoV-2 vaccines. Further studies are needed to explore the mechanism of TED following mRNA SARS-CoV-2 vaccination, risk factors, prevention and treatment.

Introduction

SARS-CoV-2 vaccination and infection have been linked to a number of autoimmune and inflammatory diseases, including thyroid dysfunction[1-4]. Both Graves' disease (GD) and non-thyroidal ocular manifestations have been reported after administration of the SARS-CoV-2 vaccine[5-7]. However, little is known about thyroid eye disease (TED) in relation to exposure to SARS-CoV-2 vaccination.

Thyroid eye disease is a debilitating and potentially sight-threatening condition. 90% of patients with TED have hyperthyroidism and about 10% are euthyroid or hypothyroid[8]. Of the patients with GD, up to 40% can develop TED[9]. The disease involves an active inflammatory phase that can last 6-36 months followed by a stable inactive chronic phase[10]. Clinical evaluation of TED patients involves assessment of the activity and severity of their disease. Activity is assessed through the clinical activity score (CAS), which measures inflammatory signs and symptoms, with a score of ≥3/7 at presentation or ≥4/10 at follow-up, reflecting active disease[11]. Severity is determined by the degree of proptosis, diplopia, and soft tissue changes and their impact on quality of life[12]. Risk factor control, steroids and orbital radiation have been the traditional treatments of active moderate/severe TED in the past, while biologics such as tocilizumab and rituximab have been tried with limited success[13-16]. The insulin growth factor-1 receptor (IGF-1R), which forms a complex with the thyroid stimulating (TSH) receptor, has recently been shown to play an important role in the pathogenesis of TED, by mediating activation of orbital fibroblasts in response to TSH receptor stimulating antibodies[17]. Teprotumumab, an antagonist of the IGF-1R, has become the first therapeutic agent approved by the FDA for treatment of TED, after two RCTs demonstrated its significant efficacy in improving proptosis, diplopia, and QoL in TED patients[18,19].

Despite these advances in treatment, the exact etiology of TED remains elusive. Even though genetic susceptibility plays an important role in the pathogenesis, epigenetic changes and environmental factors are also thought to be involved[14,20]. There are a number of known risk factors for TED, which include female gender, advancing age, tobacco smoking, uncontrolled thyroid disease, elevated TSH receptor antibodies, radioactive iodine treatment, vitamin D deficiency and potentially hypercholesterolemia[20-25]. Recent studies have also supported a role for epigenetic changes and microbiome imbalance in TED pathogenesis through the impact of gut microorganisms on

the immune repertoire and the balance between regulatory T cells and T helper17 lymphocytes[20,26]. Other factors that affect the immune landscape may also influence TED pathogenesis[27]. In this report, we describe two cases of TED activation following mRNA SARS-CoV-2 vaccination and review all COVID-19-vaccination-associated TED that have been published to date.

Materials and Methods

We describe two cases that presented to the endocrine clinic with worsening or new onset TED following SARS-CoV-2 vaccination. We obtained demographic data, COVID vaccination history, thyroid disease and TED history from the patients' medical records and continued to follow their course of disease and response to therapy. We also conducted a literature search for SARS-CoV-2 vaccine-related TED case reports/series published until June 2022 in the PubMed online database and Google Scholar using the following search string: (‘'Graves" OR ″orbitopathy" OR ″thyroid eye disease") AND (‘'COVID-19″ OR ″SARS-CoV-2″) AND (‘'vaccine" OR ″immunization").

Results

Case 1

A 50-year-old non-smoker male, with a history of psoriasis, vitiligo, and atrophic gastritis, was diagnosed with GD in March 2019 and treated with methimazole. In April 2020, he developed TED with bilateral proptosis, pain, edema, and diplopia. His CAS was 6/7. Following a 3-month course of oral methylprednisolone, at a dose of 48 mg per day, he showed limited response and developed severe side effects. He underwent total thyroidectomy in November 2020. Six weeks after the operation, his TED improved (CAS 4/10), without significant improvement in proptosis, thyroglobulin was low at 3.09 ng/ml, and thyroid stimulated immunoglobulin (TSI) levels normalized from 4.13 IU/l six weeks prior to surgery to 0.70 IU/l (reference< 1.75 IU/l). In January 2021, he received 2 doses of the mRNA BNT162b2-SARS-CoV-2 vaccine (Pfizer-BioNTech). Three weeks after the second dose, his TED symptoms significantly worsened with severe eye pain, eyelid edema, conjunctival erythema, worsening proptosis and diplopia, and swelling of the conjunctiva and caruncle (CAS 7/10) (Fig. 1A). TSI levels rose to 4.45 IU/l, while patient was euthyroid on levothyroxine (TSH 2.3 mIU/L). He received 12 weekly methylprednisolone infusions (cumulative dose of 4.5 g) with limited response. He was then treated with three monthly cycles of intravenous tocilizumab with remission of inflammation of caruncle, but otherwise limited improvement in eyelid swelling and pain, and no effect on proptosis and diplopia (CAS 6/10). Severe arthralgias and intractable pruritus necessitated

discontinuation of tocilizumab treatment. The patient then received a full course of treatment with teprotumumab, with 8 infusions at 3-week intervals. Significant clinical improvement was noted after the third teprotumumab infusion, leading to an excellent overall response over a 24-week period, as evidenced by significant decrease in eyelid swelling/pain, improvement in diplopia, and decreased CAS score from 6/10 to 3/10, in view of 5 mm improvement in proptosis and resolution of conjunctival redness and swelling (Fig. 1B).

Case 2

A 71-year-old non-smoker female had a 40-year history of hypothyroidism, controlled on levothyroxine. In March 2021, three days after her second dose of the mRNA-1273 SARS-CoV-2 vaccine (Moderna 0.5ml), she developed bilateral eye swelling and burning. She initially received antihistamines and steroid eye drops without improvement. She also experienced a 20 Ib weight loss, palpitations, tremors and heat intolerance. By August 2021, her eyes further deteriorated with eye pain, redness, lid edema and erythema, diplopia, and worsening proptosis (CAS 4/7, Fig. 2A). TSI index was 5.5 (reference ≤1.3), TSH was undetectable, FT4 1.4 ng/dl (reference 0.93-1.70 ng/dL), and FT3 3.9 pg/ml (reference 2.3-4.2 ng/dL); levothyroxine was discontinued. Orbital CT showed enlargement of the extraocular muscles bilaterally and mild bilateral exophthalmos (Fig. 3). Two weeks later she was admitted to the hospital with loss of color vision (Ishihara color plates 0/14 in right eye and 4/15 in left eye) and decreased visual acuity in the right eye. She received two doses of 1 g intravenous methylprednisolone, followed by intravenous teprotumumab on hospital day 3. She responded well to teprotumumab infusions every three weeks, with return of color vision (Ishihara color plates 14/14 in both eyes) and improvement of proptosis and periorbital edema (CAS 1/10) after her third teprotumumab infusion in October 2021 (Fig. 3B). By that time, her TSH was 5.8 IU/mL (reference 0.27 - 4.20 IU/mL), FT4 0.98 ng/dl and TSI 4.6 and she was restarted on low dose levothyroxine. She received her Moderna booster vaccine (0.25 ml) in November 2021, one week before her 4th teprotumumab infusion, with no reported eye symptom flare or complications, and completed a total of eight teprotumumab doses in February 2022.

Literature review

Characteristics of patients with TED associated with mRNA SARS-CoV-2 vaccination

In addition to the two cases we described, eight TED cases associated with SARS-CoV-2 mRNA vaccination have been reported in the literature to date (Table 1). Of all 10 cases, eight were females, six had no smoking history and the mean age was 54 years. Two cases had Hashimoto's thyroiditis, whereas six cases had a known history of

Graves' disease with duration ranging from 2-16 years. Four out of total 10 cases had new onset of TED shortly after vaccination, whereas six cases had a history of stable TED diagnosed 9 months to 20 years prior to SARS-CoV-2 vaccination. Of the cases with prior TED history, one patient had a past history of dysthyroid optic neuropathy (DON) which was treated with intravenous methylprednisolone and teprotumumab a year before. Six patients received the Pfizer SARS-CoV-2 mRNA vaccine and four patients the Moderna Vaccine. The time of TED symptom onset ranged from one day after the first dose to three weeks after the second vaccine dose.

Severity and management of TED associated with mRNA SARS-CoV-2 vaccination

Active TED after mRNA SARS-CoV-2 vaccination had a wide range of severity. Most cases had moderate/severe active disease requiring treatment, two cases were mild/moderate, while two cases progressed to DON. The management of TED after vaccination had variable response to different treatments. Seven cases were successfully treated with teprotumumab, showing significant favorable response as early as after the first two doses. One of these cases, case 1 described above, showed very little improvement on glucocorticoids, with some response to tocilizumab which was limited to soft tissue swelling. In case 8, the patient had reactivation of TED that progressed to DON and had a temporary response to oral prednisone, but eventually required orbital decompression[31]. The two latter cases were eventually treated and responded well to teprotumumab[31]. In case 2, new onset TED progressed to sight-threatening orbitopathy requiring two doses of IV methylprednisolone immediately followed by teprotumumab. Only two cases had mild TED that did not require any treatment[28,30].

Discussion

In contrast to the numerous cases of post-SARS-CoV-2 vaccine thyrotoxicosis that have been reported due to new-onset/relapse of Graves' disease or subacute thyroiditis, there is scant literature linking m-RNA vaccines for SARS-CoV-2 to TED[5,33,34]. In addition to the two new cases we describe here, eight TED cases associated with SARS-CoV-2 mRNA vaccines have been published. Although incidental TED presentation is possible, the temporal sequence in combination with the short interval of TED development or deterioration after vaccine administration and the lack of other typical apparent triggers, including dysthyroidism, new smoking, or radioactive iodine exposure prior to presentation, strongly suggest a pathogenetic link. This is also supported by existing literature describing SARS-CoV-2 vaccine as a trigger for other autoimmune diseases, especially in individuals with immune dysregulation and genetic predisposition[1].

The mRNA SARS-CoV-2 vaccines were the first mRNA vaccines to receive FDA approval and have been used in a large scale around the globe[34]. To date there have been no reported TED cases after non-mRNA SARS-CoV-2

vaccines or other conventional vaccines. Interestingly, there has been one case report of GD and TED activation following SARS-CoV-2 infection[35]. Postulated mechanisms for the link between vaccination and Graves' disease include direct activation of angiotensin-converting enzyme 2 (ACE-2) receptors in the thyroid gland, cross-reactivity of vaccine components with thyroid antigens, vaccine-related lymphocyte activation, and induction of autoimmunity by vaccine adjuvants resulting in the autoimmune/inflammatory syndrome (ASIA) [36,37]. Molecular mimicry between vaccine components and thyroid proteins may cause an autoimmune response in susceptible individuals[38]. The thyroid peroxidase (TPO) antigen was found to have significant (50-70%) peptide epitope sequence homology and cross reaction with the SARS-CoV-2 spike protein, nucleoprotein and membrane proteins[38]. Antibodies against these viral targets may therefore cause thyroid tissue damage, leading to release of further autoantigens, and potential development of other autoantibodies such as TSI, that may trigger TED[39]. In our case 1, it is possible that there was residual thyroid tissue or thyroglossal duct remnant following the thyroidectomy, that could have served as an immune target. Another proposed mechanism is the activation of autoreactive T cells through non-antigen dependent polyclonal immune cell stimulation, either by vaccine adjuvants or inflammatory response molecules including cytokines, interferon, and toll like receptors[40]. This can result in further amplification of the inflammatory response leading to macrophage infiltration of tissues, as well as tissue fibroblast and adipocyte differentiation, all of which are processes seen in TED[17]. Orbital fibroblasts are more susceptible to inflammatory stimuli compared with fibroblasts in other tissues, as their upregulation of CD40 makes them targets for activation by CD40L on T lymphocytes[41]. Finally, it is possible that epigenetic changes or alterations in the patient's microbiome, such as those demonstrated following mRNA SARS-CoV-2 vaccination, play a role in TED pathogenesis[20,26,42-44]. The patient's underlying gut microbiome composition may also modify the risk of TED following vaccination, similar to the way it affects mRNA SARS-CoV-2 vaccine immunogenicity and adverse effects[45]. Further studies to identify the exact mechanisms of new onset TED and disease reactivation following mRNA SARS-CoV-2 vaccine are needed.

In this case series, when new onset TED was seen in patients with no history of thyroid disease or previous TED, it was relatively milder than in cases with either previous TED or known thyroid autoimmune disease. If untreated, TED can progress to DON, as was described in cases 2 and 10. The majority of mRNA SARS-Cov-2 vaccine-associated TED cases had a favorable response to teprotumumab, including two patients with DON. Two cases showed limited response to oral prednisone and the combination of methylprednisolone and tocilizumab, but then responded more favorably to teprotumumab, while a third case had 2 doses of IV methylprednisolone followed by teprotumumab with also a favorable response. Despite teprotumumab's efficacy in TED management, its availability

remains very limited, especially outside the United States due to its prohibitive cost, and there is a need for close monitoring for potential adverse events. Further studies are needed to determine the most effective treatment regimen for patients with TED activation following mRNA SARS-CoV-2 vaccination and identify potential methods of prevention. Finally, it is unclear if these patients remain at risk of TED reactivation after future mRNA SARS-CoV-2 vaccine administration and if further doses of SARS-CoV-2 vaccines can be safely administered, as has been suggested for vaccine-related thyroiditis and Graves' disease[46]. It is encouraging that our second case received an mRNA SARS-CoV-2 booster vaccine while on teprotumumab therapy and no changes were noted in her TED or thyroid status.

In this report, we summarize two new cases along with the data from existing published cases of TED following mRNA SARS-CoV-2 vaccination. These findings can help guide clinicians on early recognition, prompt reporting, and appropriate referral pathways for mRNA SARS-CoV-2 vaccine-related TED. Furthermore, they invite further research into the prevalence of TED exacerbation after SARS-CoV-2 vaccination, identification of risk factors, and development of strategies for effective treatment and prevention.

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Data availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

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Figure 1.A. Case 1 eye findings three weeks after the second dose of SARS-CoV-2 vaccination with eye pain, eyelid edema, conjunctival erythema, worsening proptosis and diplopia, and swelling of the conjunctiva and caruncle, CAS 7/10.

Figure 1.B. Case 1 eye findings after completion of 8 teprotumumab infusions with decrease in eyelid swelling/pain, CAS 3/10.

Figure 2.A. Case 2 eye findings upon presentation to clinic with eye pain, redness, lid edema and erythema, CAS 4/7.

Figure 2.B. Case 2 eye findings after the third teprotumumab infusion, with only periorbital edema, CAS 1/10.

Figure 3. CT orbits showing extra-ocular muscle hypertrophy and crowding. **A.** coronal section, **B.** transverse section.

Table 1. Characteristics, management, and outcomes of reported TED cases associated with SARS-CoV-2 mRNA vaccines.

1

2 Table 1. Characteristics, management, and outcomes of reported TED cases associated with SARS-CoV-2 mRNA vaccines.

3

	Age	Gender	Smoking status	History of thyroid disease prior to vaccine (type, duration, and management)	Anti-thyroid antibodies (type, level, and reference range)	Hx of TED prior to vaccine (known history, duration, management, CAS* after management and prior to vaccine)	Vaccine type	TED presenting symptoms	TED symptoms' onset	CAS* and TED severity at presentation	TED management	TED outcome
Case 1 (described above)	50	Male	Non smoker	Graves' disease, 22 months, methimazole followed by thyroidectomy and levothyroxine	TSI, 4.13 IU/l (< 1.75 IU/l)	Known history of TED, 9 months, received 3 months oral prednisone, stable CAS 4/10	mRNA BNT162b2-SARS-CoV-2 (Pfizer)	Severe eye pain, lid swelling, conjunctival erythema, swelling of conjunctiva and caruncle, worsening proptosis and diplopia	3 weeks after dose 2	CAS 7/10 Moderate-severe	IV methylprednisolone for 12 weeks, tocilizumab 3 monthly cycles, teprotumumab 8 infusions	Partial response CAS 5/7 with steroids/tocilizumab Good response CAS 3/7 with teprotumumab
Case 2 (described above)	71	Female	Non smoker	Hashimoto's thyroiditis, 40 years, levothyroxine	Anti-TPO, 9 (<9 IU/mL) TSI, 5.5 (reference ≤1.3)	No known history of TED	mRNA-1273 SARS-CoV-2 (Moderna)	Bilateral proptosis and burning, deteriorating to eye pain, redness, lid edema and erythema, diplopia, worsening proptosis	3 days after dose 2	CAS 4/7 Moderate-severe, progressed to sight-threatening disease	IV methyprednisone 2 gm, teprotumumab	Excellent response CAS 1/7 at 2 months
Case 3 [28]	66	Female	Non smoker	Graves' disease, 15 years, radioactive iodine (RAI) followed by levothyroxine	TSI, 3.91 IU/L (reference not reported) TRAb, 5.51 IU/L (reference not reported)	Known history of TED, over 20 years, stable for 15 years, s/p bilateral orbital decompression and strabismus surgeries, CAS not reported	mRNA-1273 SARS-CoV-2 (Moderna)	New-onset diplopia, bilateral proptosis, mild conjunctival injection, pain with eye movement	3 weeks after dose 2	CAS 6/10 Moderate-severe	Teprotumumab	Symptoms improving at 5 months after starting teprotumumab
Case 4 [28]	53	Female	Non smoker	No known history of thyroid disease	TSI, 3.21 IU/L (reference not reported)	No known history of TED	mRNA BNT162b2-SARS-CoV-2 (Pfizer)	Proptosis, bilateral periorbital edema, eye pain with movement, occasional diplopia	24 hours after dose 1	CAS 2/7 (calculated[6], not reported) Moderate-severe	Teprotumumab	Symptoms improving at 8 months
Case 5 [28]	45	Female	Non smoker	Hashimoto thyroiditis, more than 5 years	Not reported	Known history of TED, stable more than 5 years, CAS not reported	mRNA-1273 SARS-CoV-2 (Moderna)	Lid edema, trace proptosis, eyelid retraction	3 weeks after dose 1	CAS 1/7 (calculated[6], not reported) Mild	None	Resolved without treatment
Case 6 [29]	50	Female	Non smoker	Graves' disease, 12 years, RAI (time not reported) followed by levothyroxine	TSI, 2.29 (0–0.55 IU/l)	No known history of TED	mRNA BNT162b2-SARS-CoV-2 (Pfizer)	Eye irritation, tearing, pain, proptosis. In 2 months, TED further worsened with reduced eye abduction, pain with eye movement, eyelid edema, erythema, chemosis, conjunctival injection	3 days after dose 2	CAS 5/7 Moderate-severe	Teprotumumab	Had significant improvement and reduction of proptosis after the second dose
Case 7[30]	51	Female	Not reported	No known history of thyroid disease, later	Anti-TPO, 12.4 IU/ml (0–34 IU/ml)	No known history of TED	mRNA BNT162b2-SARS-CoV-2	Proptosis, irritation, dryness	4 days after dose 2	CAS 3/7*	None	Ocular findings showed a significant regression after total thyroidectomy

				found to have PTC	Anti-Thyroglobulin, 18.2 IU/ml (0–115 IU/ml) TRAb, 5.04 IU/L (<1.5 IU/L)		(Pfizer)			Mild-moderate		
Case 8 [31]	51	Female	Former smoker	Graves' disease (details unknown)	Not reported	Known history of TED, 16 years, DON treated with oral prednisone, IV methylprednisone, s/p right orbital decompression and multiple eyelid surgeries followed by teprotumumab, completed 30 weeks prior to vaccine, CAS 1/10	mRNA-1273 SARS-CoV-2 (Moderna)	Symptoms not specified	2 weeks after dose 2	CAS 9/10 Severity not reported	Oral prednisone, teprotumumab 8 infusions, bilateral orbital decompression	Symptoms persisted on prednisone. No active TED 13 months after teprotumumab and 2 months after orbital decompression
Case 9 [32]	58	Female	Not reported	Graves' disease, 3 years, underwent RAI 2 years ago	TRAb, 6.82 IU/L (0–1.5 IU/L)	Known history of TED, 2 years, IV methylprednisone, CAS 3/7	mRNA BNT162b2-SARS-CoV-2 (Pfizer)	Chemosis, redness of eyelids and conjunctiva, periorbital edema, pain and foreign object sensation in the eyes, diplopia	3 days after dose 2	CAS 6/10 Moderate-severe	Planned for teprotumumab	Not reported
Case 10 [32]	43	Male	Not reported	Graves' disease, 1 year, methimazole	TRAb, 20.7 IU/L (0–1.5 IU/L)	Known history of TED, 1 year, IV methylprednsione 12 months and external orbital radiation 10 months prior, CAS 4/7	mRNA BNT162b2-SARS-CoV-2 (Pfizer)	Proptosis, abduction deficit, diplopia, bilateral keratopathy, lagophthalmos, abduction deficit	2 weeks after vaccine administration (dose not specified)	CAS 8/10 Moderate-severe	Not reported	Not reported

*The Clinical Activity Score (CAS) ranges from 0 to 10. A 7-point scale is used when no previous assessment is available per American Thyroid Association guidelines[6].

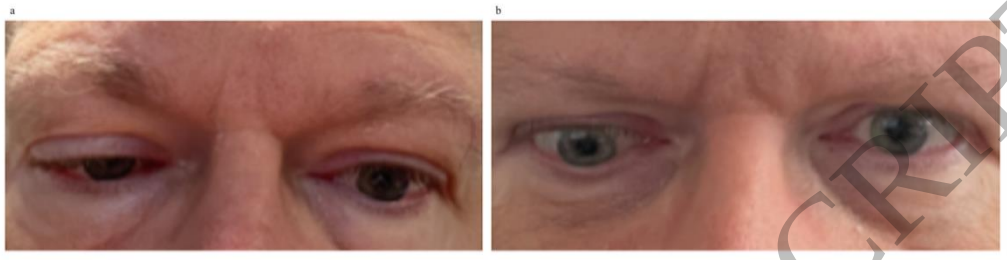

Figure 1
82x51 mm (1.7 x DPI)

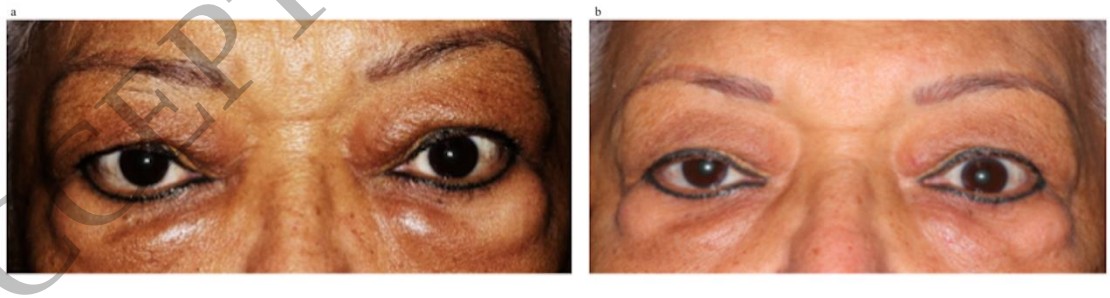

Figure 2
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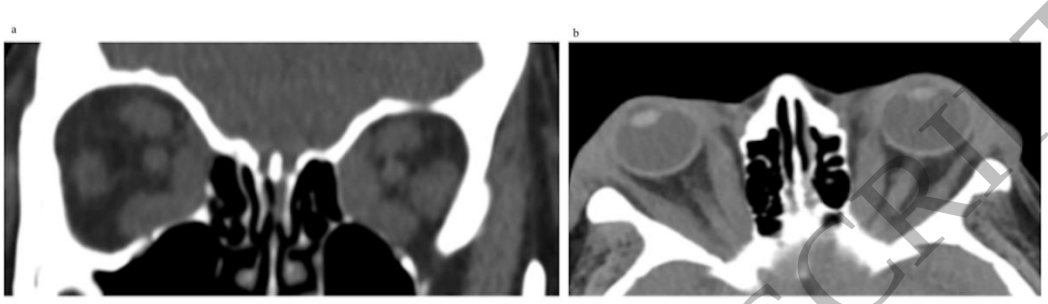

Figure 3
82x51 mm (1.7 x DPI)