vaccination or exposure to *Mycobacterium species* might be involved in modulating autoimmune responses towards the thyroid gland. Our study warrants further research on the immunomodulatory role of BCG in adult subjects with a family history of autoimmune diseases including AITD.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Evaluation of TRAb and TSI Leves and Thyroid Function in Pregnant Women With Graves' Disease and Newborn: Preliminary Data

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Introduction: GD, mediated by TSH receptor-stimulating immunoglobulins (Igs) (rTSH), can lead to fetal thyroid dysfunction through the passage of Igs through the placenta during pregnancy. TRAb levels, used for prognostic evaluation, measure rTSH-stimulating and blocking Igs while TSI evaluates only as stimulating Igs. Objective: To prospectively evaluate pregnant women with DG and newborns (NB) by measuring TRAb and TSI and their correlation with thyroid function and postpartum complications. **Methods:** The patients were evaluated during pregnancy and the puerperium and the respective newborns. TSH, thyroid hormones and TRAb were evaluated by electrochemiluminescent method (Roche) and TSI by chemiluminescent assay (Siemens). TRAb<1.75IU/L and TSI<0.55IU/L were considered negative. **Results:** Nine patients were evaluated, with a mean age of 27.4±5.7 years: 6 had TRAb and TSI positive in the 1st trimester (1st-tri), when they maintained or started DAT; one with both negative (without DAT) and one with weakly positive TSI, when DAT was suspended. These last two remained euthyroid during pregnancy and puerperium. Of the first 6, 4 were evaluated in the 3rd-tri: three negative for TRAb and maintained positive TSI, 2 in low leves and one for high titles, when DAT was suspended or reduced; one kept both at very high levels. A patient with post-DT hypothyroidism, performed 3 years ago, using levothyroxine, evaluated in the 3rd-tri, had a negative TRAb and a highly positive TSI and remained so after pregnancy. The two patients who presented weakly positive TSI in the 3rd-tri evolved with their negative results and without DAT in the puerperium. The patient with TSI in high titers evolved with elevated levels as well as positive TRAb titers and postpartum decompensation. The patient with positive antibodies remained compensated for stable doses of DAT. Four NB were evaluated: all healthy, with normal thyroid function and negative TRAb. TSI was positive in 2 in the postpartum period; TSI was negative afterwards, while in the other 2 both antibodies were negative. **Conclusions:** TSI was not associated with thyroid dysfunction in NB, although it was associated with worsening hyperthyroidism in pregnant women, when at high titers. Positive TSI at low levels were not associated with worsening of the condition, which requires further studies to determine the cutoff point for assessing treatment suspension.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Hearing Loss and Teprotumumab

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Thyroid eye disease (TED) is an unpredictable autoimmune inflammatory disease which can be sight-threatening, debilitating, and disfiguring. Teprotumumab (IV infusion every 3 weeks x 8 doses) was recently approved as the first and only FDA-approved drug for TED in 2020. Phase 2 and 3 studies showed significant improvement in proptosis, double vision, soft tissue inflammation and quality of life for patients with active moderate to severe TED. Side effects were experienced by 85% of patients on teprotumumab. Hearing loss symptoms were reported in 10% of patients and were reported to be reversible upon stopping the drug. Objective: To explore the incidence of hearing loss symptoms and sensorineural hearing loss in patients treated with teprotumumab. **Methods:** All patients, followed at one institution, treated with at least 4 infusions of teprotumumab were evaluated. Charts were evaluated for baseline hearing symptoms and hearing symptoms during or after therapy with teprotumumab. Those patients with hearing symptoms were referred for audiogram testing and patulous eustachian tube (PET) testing. **Results:** Twenty-eight patients were included in this analysis. Thirteen patients (46%) complained of hearing symptoms. The most common symptoms were autophony or an ear plugging sensation and hearing loss or muffled hearing. Hearing symptoms developed after a mean of 3.6 infusions. Of the patients with hearing symptoms, three patients (23%) had sensorineural hearing loss documented on audiogram (n=2) or patulous eustachian tube (n=1) documented on PET testing. To date, the patient with PET has experienced some improvement, but not resolution, of her symptoms. The two patients with documented sensorineural hearing loss have not experienced a significant improvement in hearing, on audiogram, on average 3 months after stopping teprotumumab. **Conclusion:** Teprotumumab is a promising new therapy for active moderate to severe thyroid eye disease. Providers should consider performing a baseline audiogram with PET testing and performing audiograms with PET testing for patients that develop hearing symptoms during or after therapy. Hearing loss is a concerning adverse event and its mechanism and reversibility should be further studied.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Identification of RORg$^+$T Cells as Key Players in Thyroid Autoimmunity From Checkpoint Immunotherapy

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Purpose: Immune checkpoint inhibitors (ICI) are powerful new cancer therapies that leverage the body's own immune system to attack cancer cells. Unfortunately, their use may be limited by the development of immune-related adverse events (IrAE) in up to 60% of patients. Thyroiditis is a common IrAE, with shared and distinct features from spontaneous thyroid autoimmunity, *i.e.* Hashimoto thyroiditis (HT). The cause of IrAE remains unknown, however, recent data suggest that toxicity can be uncoupled from anti-tumor effects.

Methods: We developed a novel mouse model to study mechanisms of IrAE, in which ICI (anti-PD-1 and/or anti-CTLA-4) treatment leads to multi-organ immune infiltrates, including thyroiditis. To understand immune changes occurring with ICI-autoimmunity, we first evaluated changes in the frequency and activation status of different immune cells in our mice using immunohistochemistry (IHC) and flow cytometry. Then we confirmed these findings in peripheral blood and thyroid fine needle aspiration (FNA) specimens from patients with ICI-thyroiditis, HT, or no IrAE, using flow cytometry and single cell RNA sequencing (scRNAseq) techniques.

Results: In our mouse model, ICI treatment of autoimmune-prone non-obese diabetic mice induces multi-organ autoimmunity. Modeling ICI-IrAE observed in humans, our mice developed increased immune infiltrates in multiple tissues (*e.g.* thyroid, colon, liver, lung), autoantibodies, and acceleration of underlying autoimmune risk (*i.e.* diabetes). Increased frequency of autoimmune disease was seen with combination (anti-PD-1 + anti-CTLA-4) *vs.* single agent ICI. We found increased IL-17A$^+$ T cells in secondary lymphoid tissues of ICI-treated mice, a cytokine produced by RORγ^+ Th17 and Tc17 cells and associated with autoimmunity. IHC studies on thyroid infiltrates showed accumulation of CD4$^+$ and CD8$^+$ T cells and macrophages in ICI-treated *vs.* isotype control mice. This finding was confirmed by flow cytometry analyses of thyroid-infiltrating leukocytes in ICI-thyroiditis mice, which showed significantly increased T cells, specifically RORγ^+ T cells, and rare B220$^+$ B, CD11b$^+$ myeloid, or NKp46$^+$ NK cells. In patients with ICI-thyroiditis, thyroid FNA showed that thyroid immune infiltrates were predominately T cells. scRNAseq studies in patients with ICI-thyroiditis showed enrichment of Th17 and Tc17 (RORγ^+ IL23R$^+$ CD161$^+$) T cells, compared to ICI-treated patients without IrAE.

Conclusion: We have identified a role for RORγ^+ Th17 and Tc17 cells in thyroid autoimmunity from ICI using a newly developed mouse model of ICI-associated IrAE and translational studies in patients with ICI-thyroiditis. Th17 and Tc17 cells have previously been associated with spontaneous autoimmune disease, including HT, but have not yet been characterized in IrAE. These cells provide a potential therapeutic target for prevention of endocrine IrAE from ICI.

Thyroid

THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

Insights From Prospective Follow-up of Thyroid Function and Autoimmunity Among Covid-19 Survivors

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Objective: Occurrence of Graves' disease and Hashimoto's thyroiditis after coronavirus disease 2019 (COVID-19) raised the concern about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggering thyroid autoimmunity. Uncertainties remain regarding incident thyroid dysfunction and autoimmunity among COVID-19 survivors. We carried out a prospective study to characterize the evolution of thyroid function and autoimmunity among COVID-19 survivors. **Method:** Consecutive adult patients, without known thyroid disorders, admitted to Queen Mary Hospital for confirmed COVID-19 from 21 July to 21 September 2020 were included. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3) and anti-thyroid antibodies were measured on admission and at 3 months. Positive anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) was defined by >100 units. **Results:** Among 200 COVID-19 survivors, 122 had reassessment thyroid function tests (TFTs) (median age: 57.5 years; 49.2% men). Baseline characteristics of patients who did and did not have reassessment were comparable. Among the 20 patients with baseline abnormal TFTs on admission, mostly low fT3, 15 recovered. Of the 102 patients with normal TFTs on admission, two (2.0%) had new onset abnormal TFTs, which may represent TFTs in different phases of thyroiditis (one had mildly elevated TSH 5.8 mIU/L, with normal fT4 [16 pmol/L] and fT3 [4.3 pmol/L], the other had mildly raised fT4 25 pmol/L with normal TSH [1.1 mIU/L] and fT3 [4.7 pmol/L]). Among 104 patients with anti-thyroid antibody titers reassessed, we observed increases in anti-TPO (baseline: 28.3 units [IQR 14.0-67.4] vs reassessment: 35.0 units [IQR: 18.8-99.0]; p<0.001) and anti-Tg titers (baseline: 6.6 units [IQR 4.9-15.6] vs reassessment: 8.7 units [IQR: 6.6-15.4]; p<0.001), but no change in anti-TSHR titer (baseline: 1.0 IU/L [IQR: 0.8-1.2] vs reassessment: 1.0 IU/L [IQR: 0.8-1.3]; p=0.486). Of the 82 patients with negative anti-TPO at baseline, 16