Delayed diagnosis of severe secondary hypothyroidism in a patient presenting with mixed hyperlipidaemia and a metabolic myositis

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Presenting complaint

A **51** year old South Asian woman was referred by her GP to the outpatient endocrine clinic **with diffuse musculoskeletal pains** in her lower limbs, **lethargy** and **weight gain** in the context of a **previous hemithyroidectomy**

Past medical history

1) Right hemithyroidectomy (*for histologically benign thyroid nodule*)
2) Obesity – BMI 33.3
3) Hypercholesterolaemia

Drug history

1) Ferrous Fumerate 210mg TDS
2) Non-smoker
3) Minimal ETOH consumption
4) NKDA

Family history

Father – CVA in his 50s
Mother – Deceased; complications of TB
Sister – T2DM
Brother – HTN / hypercholesterolaemia

Social history

Works in customer services
2 school-age children

Further history of presenting complaint

Further history revealed intermittent pains in both lower limbs for several months; primarily left knee and right ankle. This was associated with 5kg of unintentional weight gain.. The patient also had a new diagnosis with hypercholesterolaemia from her GP 9 months ago that was being managed with lifestyle interventions in the first instance. She reported feeling increasingly lethargic for many months but this hasn't affected her ability to undertake her job or activities of daily living

Initial biochemistry

TSH 3.21 [0.4 – 4.5 mU/L]
Creatine Kinase 1950 [24 – 170 U/L]
Total cholesterol 9.5 [<5.5 mmol/L], LDL 6.5 [<3 mmol/L], HDL 1.40 [>1.0 mmol/L], Triglyceride 3.5 [<1.7 mmol/L]
Hb 106g/L, MCV 86 fL, Ferritin 60 ug/L
B12, Folate, Vitamin D, U&Es, LFTs - Normal

Initial review

BP 113/73mmHg, weight 74.9kg, height 1.50, BMI 33.3
Clinical examination: right hemithyroidectomy scar, no goitre. Diffuse muscular tenderness, no signs of synovitis.

Referred to Rheumatology clinic for investigation of elevated CK (who planned an EMG and muscle biopsy).
For annual follow-up in endocrine clinic

Interval biochemistry

TSH 2.59 [0.4 – 4.5 mU/L], Free T4 1.7 pmol/L [9 – 25] ,
Free T3 1.3 pmol/L [3.5 – 7.8]
U&Es normal, Lipid Profile unchanged, Glucose 5.4

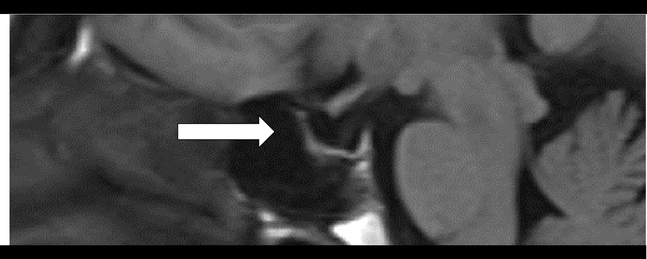
Unexpected severe secondary hypothyroidism
TSH inappropriately normal in face of low free T4

Further work-up – pituitary profile and history

Has had two children, breastfed on both occasions (9 months, 3 months).
No issues with postpartum haemorrhage. No problems with milk supply
No history of head injury. Period stopped ~40 years old.
Short Synathen Test: Baseline 145nmol /L [170], 30 mins: 415nmol/L, 60 mins 525nmol/L [580]
IGF-1 2.4 nmol/L [6.2 – 26.3], Prolactin 9 mU/L [40 – 530]
FSH 3.4 iU/L [23 – 116], LH 1.4 iU/L [17 – 75]

Further work-up – MRI pituitary

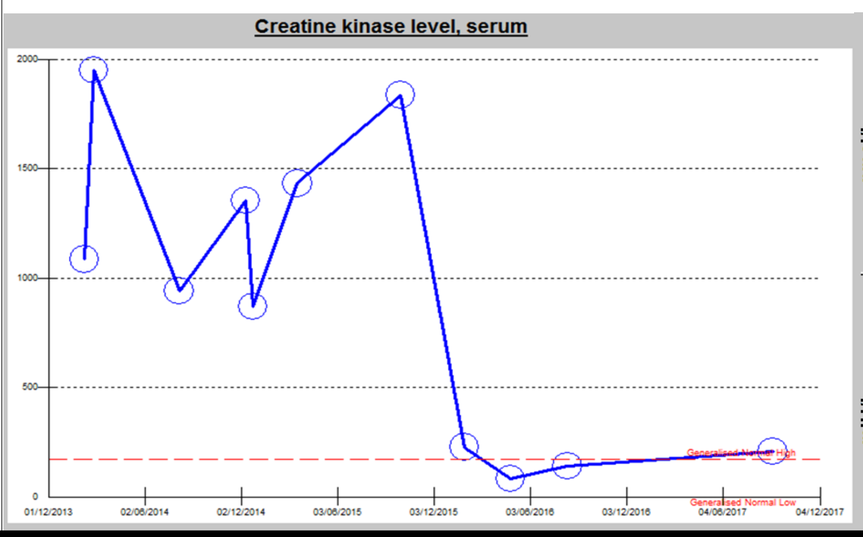
"The patient has an empty sella. No pituitary tissue is demonstrated. There is no enhancing mass. The pituitary stalk appears normal. The pituitary fossa is not expanded."

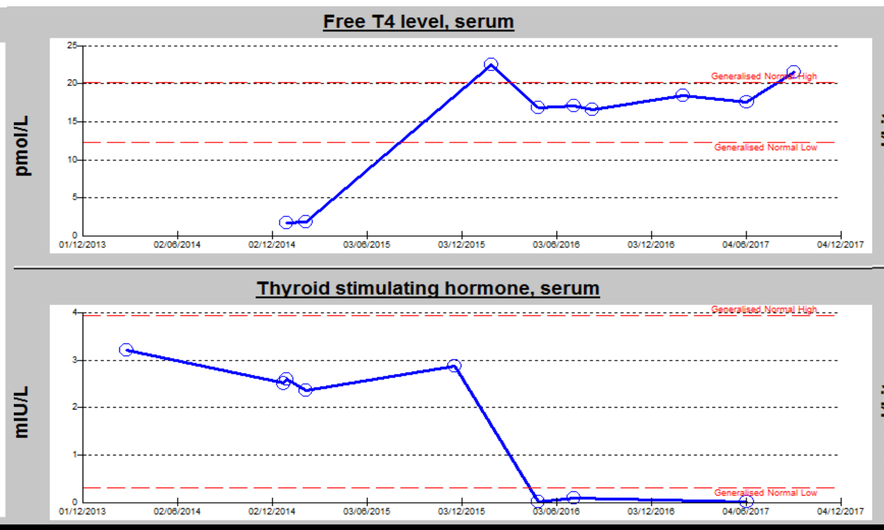


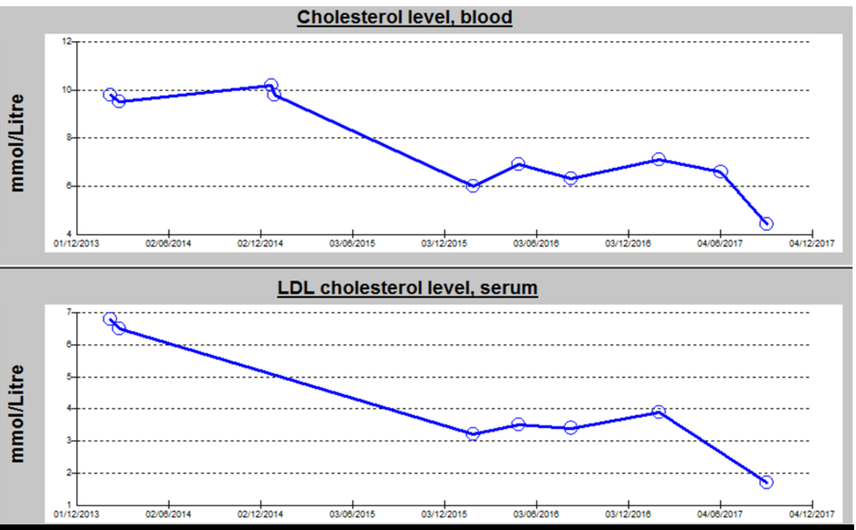
Diagnosis and management

Diagnosis: Panhypopituitarism with a metabolic myositis and dyslipidaemia

Commenced on thyroid hormone replacement which was subsequently uptitrated to 100 micrograms per day and hydrocortisone replacement therapy (10mg, 5mg, 5mg)
Over the following 9-12 months there was almost a complete resolution of the metabolic myositis and dyslipidaemia as shown on the graphs below
Subsequently, the patient experienced exertional chest pains prompting a cardiology referral. Work-up has revealed stenosis within the LAD awaiting percutaneous intervention.







TSH and T4 – paired testing

In 2006 guidelines were published by the *British Thyroid Society* summarising recommendations with regards to the biochemical diagnosis and monitoring of thyroid disorders. [3]
It is noted that the strategy of first-line measurement of TSH alone is only cost effective for the purposes of screening and is inappropriate in certain clinical situations.
TSH monitoring alone would be considered appropriate post-thyroidectomy in an asymptomatic patient.
However, in the context of the signs, symptoms and biochemical abnormalities that could be precipitated by derangement of the thyroid axis, paired-testing should always performed.
The combination of weight-gain, new severe dyslipidaemia and metabolic myositis with no other clear precipitant should have prompted paired testing earlier on in the case.
Thyroid hormone replacement 18-24 months earlier could have assuaged a significant burden or cardiovascular risk.

Hypothyroid myositis

This patient demonstrates a mild hypothyroid myositis with gradual normalisation of CK upon initiation of exogenous thyroid hormone.
Musculoskeletal complaints are very common in patients with hypothyroidism; up to 79% as reported by Duyff and colleagues in a prospective cohort study although only 38% had clinical signs of weakness. [1]
Elevation of serum CK is also common in hypothyroidism with between 37%-60% having values above the upper limit of the reference range [2].
There is a poor correlation between the extent of the rise of the CK and clinical symptomology (both subjective and objective).
Generally, a CK >10 times the upper limit of normal (~2000iU/L) is thought to be of clinical significance and warrant further investigation or therapy rather than just monitoring. Without a clear aetiology for the hyperCKaemia a serum TSH would always be advised to screen for thyroid dysfunction.The pathophysiology underlying the muscle changes in hypothyroidism are well documented. Lack of bioavailable T3 leads to intracellular changes in glycogen metabolism and oxidative phosphorylation and alterations of the actin-myosin unit. Ultrastructurally changes are also seen in the membrane permeability of myocytes leading to increased enzymatic release. [2]

Hypothyroid dyslipidaemia

Dyslipidaemia is a common abnormality in patients with thyroid disease. It is the end result of thyroid hormones playing a role in multiple aspects of lipid metabolism including synthesis, mobilisation and degradation.
The most common pattern of lipid abnormalities seen in overt hypothyroidism is an increase in total cholesterol and in LDL-cholesterol. Triglycerides, HDL-cholesterol and lipoprotein may either be normal or mildly elevated. The case presented here is in-keeping with the literature. [4]
Patients with overt hypothyroidism are at significantly increased risk of cardiovascular disease. Due to the wide-ranging effects of thyroid hormones this is multifactorial. Hypothyroidism has been shown to accelerate plaque development, directly impair left ventricular function and increase total peripheral resistance. The effect of atherosclerosis is independent of the effect on lipid profile. [4]
There is little in the literature to quantify the increased risk of overt hypothyroid on cardiovascular outcomes. However, meta-analyses of cohort studies have shown sub-clinical hypothyroidism gives a relative risk of 1.21 for all-cause cardiovascular mortality in those aged <65. [5]
The risk from overt hypothyroidism is likely even greater.
I suspect hypothyroidism played a significant role in the development of this patient's early ischaemic heart disease given that she has few other conventional risk factors.

References:

[1]: *Neuromuscular findings in thyroid dysfunction: a prospective clinical and electrodiagnostic study*. J Neurol Neurosurg Psychiatry 2000;68:750–755
[2] *Hypothyroid myopathy: A peculiar clinical presentation of thyroid failure. Review of the literature*. Rev Endocr Metab Disord (2016) 17:499–519
[3] UK Guidelines for the Use of Thyroid Function Tests. http://www.btf-thyroid.org/images/documents/tft_guideline_final_version_july_2006.pdf. July 2006.
[4] *Lipid Abnormalities and Cardiometabolic Risk in Patients with Overt and Subclinical Thyroid Disease*. Journal of Lipids Volume 2011, Article ID 575840.
[5] *Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis*. Singh et al. International Journal of Cardiology, vol. 125, no. 1, pp. 41–48, 2008

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