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Case Report

A case of apathetic thyrotoxicosis: a rare presentation of hyperthyroidism in the elderly with literature review

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Introduction

Apathetic thyrotoxicosis presents with symptoms like lethargy, loss of appetite, loss of weight, apathy and depression, despite the underlying hypermetabolic state [1,2]. It is commoner among the elderly and among females, and the leading aetiology is Graves' disease [3]. The diagnosis is often delayed or missed due to the atypical presentation which leads one to suspect malignancy, psychiatric disorders or ischaemic heart disease or simply attribute the symptoms to the process of ageing.

The underlying mechanism is thought to be an age-related decrease in adrenergic tone, increased tissue resistance to catecholamines and altered neurotransmission leading to apathy [1,4].

Liver dysfunction in hyperthyroidism occurs via autoimmunity and mitochondrial dysfunction with hepatocyte apoptosis and ischaemia [5,6]. Thrombocytopaenia associated with hyperthyroidism is explained by increased platelet turnover and reduced platelet life span [8]. Hypercalcaemia and hyperphosphatemia are explained through increased bone turnover [4].

Apathetic thyrotoxicosis should be suspected in the elderly with the afore mentioned clinical features and can be confirmed with thyroid function tests. The aetiology needs to be sought for definitive treatment to improve the quality of life and minimise complications in this vulnerable population.

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Case report

A carpenter in his late sixties presented with progressive loss of appetite and weight loss of 10 kg over 3 months. He experienced nausea, regurgitation, malaise and intermittent low-grade fever. There were no drenching night sweats, respiratory symptoms, altered bowel habits or urinary symptoms. He had no history of exposure to tuberculosis or features of autoimmune diseases.

He was under treatment for diabetes mellitus, dyslipidaemia, hypertension and ischaemic heart disease for 11 years with percutaneous coronary intervention (PCI) done to the left anterior descending artery 7 years previously. He was on clopidogrel 75mg nocte, atorvastatin 20mg nocte, losartan 25mg twice per day, bisoprolol 5mg daily, metformin 500 mg twice per day and gliclazide 40mg twice per day.

He had a history of upper gastrointestinal bleeding with antral gastritis 6 years previously. He was a teetotaller and had no history of high-risk sexual behaviour.

His body mass index (BMI) was 19kg/m^2. General examination revealed a tinge of icterus and pallor without fever, lymphadenopathy or clubbing. He had no goitre or thyroid eye signs. Cardiovascular, abdominal and respiratory system examination were unremarkable.

The main differential diagnoses included malignancy, chronic infective disorders (tuberculosis, HIV) and endocrine disorders (Addison disease, hypothyroidism).

Investigations revealed mild anaemia and moderate thrombocytopenia with possible viral infection in the blood picture. The inflammatory markers, blood cultures and transthoracic 2D echocardiogram were normal.

He had a direct hyperbilirubinemia with mild hypoproteinaemia, slightly elevated aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT). Rest of his liver and renal functions were normal. The 9am serum cortisol and creatine phosphokinase were also normal. The albumin corrected serum calcium was elevated at 3.2 mmol/L with normal phosphorus, magnesium and parathyroid hormone levels.

Upper gastrointestinal endoscopy revealed pangastritis with a normal colonoscopy study. Mucosal biopsies were negative for malignancy. Contrast enhanced computed tomography of the chest, abdomen and pelvis (CECT-CAP) was unremarkable. Viral studies, auto-antibodies including anti-nuclear antibody, bone marrow biopsy, serum ferritin, lactate dehydrogenase and direct and indirect Coomb's tests were also normal.

He had a severely suppressed TSH and significantly elevated free T3 (FT3) and free T4 (FT4) values suggestive of severe hyperthyroidism. Ultrasound scan (USS) revealed a diffusely enlarged thyroid with heterogeneous echo texture with increased vascularity. Two heterogenous nodules were noted in the right lobe (1.4x0.9 cm and 1.4x1.7 cm) with increased vascularity. Fine needle aspiration cytology revealed scattered haemosiderin

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laden macrophages and a few follicular epithelial cells with blood mixed thin colloid. Thyrotrophin receptor antibody (TSH-R-Ab) was positive.

Table 1: Investigation summary

Investigation	Result	Reference range
WBC	4.94 X 10^3/ µL	4-11 X 10^3/ µL
Neutrophils	52.4%	
Lymphocytes	32.2%	
Monocytes	13.4%	
Eosinophils	2.9%	
Haemoglobin	11.9 g/dL	13.5-17.5 g/dL
Platelets	56 x 10^3 / µL	150-450 / µL
C Reactive Protein (CRP)	<2mg/L	0-5 mg/L
ESR	19 mm/1st hour	
AST	41 U/L	0-35 U/L
ALT	28 U/L	0-35 U/L
T. Bilirubin	74.1 µmol/L	5-21 µmol/L
D. Bilirubin	25.4 µmol/L	0-3.4 µmol/L
Alkaline Phosphatase (ALP)	111 U/L	47-119 U/L
GGT	67 U/L	0-49 U/L
Albumin	29 g/L	35-53 g/L
Globulin	18 g/L	
Serum ceruloplasmin	1.5 µmol/L	0.93-2.65 µmol/L
24-hour urine copper - excretion	0.27 µmol/day	0.23-1.09 µmol/day
TSH	<0.001 mIU/L	0.47-4.7 mIU/L
Free T3	19.87 pg/mL	2.6-5.4 pg/dL
Free T4	>7.77 ng/dL	0.7-1.55 ng/dL
TSH-R-Ab	5.7 U/L	<0.3 U/L

Carbimazole therapy caused a remarkable improvement in symptoms, but he required frequent dose adjustments to maintain euthyroid state due to fluctuations in TSH, FT3 and FT4 levels. Platelets ranged from 80-110 x 10^3/ µL. Therefore, the treatment was changed to radioactive iodine (RAI) followed by levothyroxine. Patient clinically improved, weight gain was noted, and thyroid functions stabilised with normalisation of the platelet count and liver profile.

Discussion

Apathetic thyrotoxicosis is a rare, but well-recognised entity among the elderly population [9,10,11]. They demonstrate negative symptoms where the usually expected features of hyperthyroidism are absent [9]. The prevalence of hyperthyroidism among elderly is about 0.5-2.3% while apathetic hyperthyroidism comprises 10-15% of them [4,12]. It is quite reasonable to expect a higher incidence due to the atypical presentation [1,9,13,14,15].

Other features of apathetic hyperthyroidism include weight loss, cardiac arrhythmias, apathy and depression [4]. The typical eye signs are rare. The skin is dry and

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hyperpigmented. Mild hypercalcemia has been reported in 20% [4] with the risk of osteoporosis and spontaneous fractures [2]. Peripheral muscle weakness, increased FT4 levels, reduced FT3/FT4 ratio, raised bone specific ALP and increased ALT levels were also noted. Hypercalcemia with elevated ALP could be due to the thyroid hormone receptors in osteoclasts and osteoblasts causing excess bone resorption. Loss of phosphorus from bone and cartilages causes high serum phosphorus levels. Thyroxine also raises the sensitivity of the beta-adrenergic receptors to catecholamines, causing hypercalcaemia and hyperphosphataemia [4].

These features of apathetic thyrotoxicosis can be easily attributed to symptoms of aging [2,13]. The diagnosis is challenging as presentations could mimic a cardiac/gastrointestinal pathology, depression or malignancy [1]. The disease process can be of greater duration (due to late diagnosis) making patients more susceptible to the complications which can be severe and fatal (atrial fibrillation, congestive heart failure, ischaemic heart disease or thyrotoxic crisis) [1,16,17].

The underlying pathogenesis is explained by age-associated reduced adrenergic tone and increased tissue resistance to the effects of thyroxine [4]. Reduced circulating catecholamines can affect neurotransmission causing apathy [1]. The use of beta blockers might have masked the tachycardia and palpitations in our patient.

Graves' disease is confirmed when there is biochemically proven thyrotoxicosis and positive TSH receptor antibodies (TSH-RA-Ab) with a hyper-vascular (thyroid inferno) and hypoechoic thyroid gland in the ultrasound scan with orbitopathy (2018 European Thyroid Association guidelines) [16]. Subacute thyroiditis was excluded due to lack of pain/tenderness of the gland, negative inflammatory markers and absence of hypo-echogenicity and hypo-vascularity [15].

Liver involvement in thyroid disease was first described in 1874. Thyroid hormones are glucuronidated and sulphated in the liver and excreted in bile. They are involved in the metabolism of bilirubin through glucuronyl transferase and ligandin. Liver dysfunction with hyperthyroidism could be solely due to hyperthyroidism, hyperthyroidism induced heart failure or concomitant liver disease. The proposed mechanisms are excess T3 induced hepatocyte apoptosis through mitochondrial dysfunction [5], hypoxic injury to hepatocytes due to increased oxygen requirement despite static splanchnic blood flow and TSH-R-Ab causing inflammatory damage to hepatocytes via the TSH receptors expressed in hepatocytes [6]. Other autoimmune conditions like primary biliary cirrhosis and autoimmune hepatitis may also contribute [5,7]. Hyperthyroidism associated liver dysfunction usually resolves when a euthyroid state is achieved [7]. It is important to identify this as most of the guidelines recommend serious reconsideration in starting anti-thyroid drugs (ATD) when the base line transaminase levels exceed five times the upper limit of normal [16,17].

Thrombocytopaenia is explained by hyper-catabolism causing accelerated platelet turnover, while antithyroid antibodies may reduce their life span [3]. Patients have a good

response when a euthyroid state is reached with anti-thyroid treatment [14 which was seen in our patient also.

Treatment of apathetic hyperthyroidism is similar to the management of typical hyperthyroidism [16,17]. Options include ATD, RAI or total thyroidectomy. Newly diagnosed Graves' hyperthyroidism in young patients is usually medically treated for 12-18 months with methimazole. If the TSH-R-Ab level is persistently elevated, treatment can be continued for another 12 months, or RAI or thyroidectomy may be considered. RAI is contraindicated in active or severe orbitopathy. It is prudent to opt for early definitive therapy with RAI in elderly patients. Older/frail patients with milder hyperthyroidism and no cardiac complications may be considered for long term ATD therapy, when other options are unavailable. We considered RAI for our patient due to significant fluctuations in the thyroid hormone levels whilst on ATD with a history of ischaemic heart disease.

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