

Case report: Heart failure from thyrotoxicosis due to Grave's disease

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Abstract

A 30-year-old female patient with a past medical history of pernicious anaemia presented with pleuritic chest pain, palpitations, fatigue, coryzal symptoms and a high temperature. She was hypoxic and tachycardic and was extensively investigated as well as aggressively treated. A type 1 'gut feeling' assessment by the admitting medical registrar made the diagnosis possible as thyroid function tests were grossly deranged and pointed to Grave's disease causing heart failure, complicated by pneumonia. The patient was discharged on carbimazole, antibiotics and beta blockers. She has now been swapped onto propylthiouracil and is under active follow up

Background

Grave's disease, named after an Irish Doctor Robert Graves, is an autoimmune disease and is the commonest cause of hyperthyroidism. Other prominent clinical features include a goitre, thyroid eye disease (Grave's orbitopathy) and pre-tibial myxoedema (a form of infiltrative dermopathy).[1,2]

There are numerous complications of Grave's disease: untreated hyperthyroidism, particularly in the elderly, can cause cardiac arrhythmias, high-output cardiac failure, osteoporosis and a thyroid storm. Vision loss secondary to orbitopathy or elephantiasis secondary to the dermopathy can also ensue. These are all associated with significant morbidity and mortality.[1,2]

Case Presentation

A 30-year-old female patient presented acutely with a short history of increased dyspnoea, fatigue, cough, left sided pleuritic pain and coryzal symptoms. She also described regular palpitations over the preceding 72 hours and intermittent high temperatures.

She was a smoker with a 10-pack year history and drank minimal alcohol. She worked in the local bingo hall and had not recently travelled. She had a past medical history of pernicious anaemia and no family history of note. She was regular vitamin B12 injections.

She was normotensive, had a heart rate of 158 beats per minute, a respiratory rate of 24 breaths per minute and oxygen saturations of 92 percent on room air. Her temperature was 38.9 degrees Celsius.

On examination, she had a normal cardiovascular, respiratory and gastrointestinal examination. There was no lymphadenopathy, clubbing, jaundice or ankle oedema.

Investigations

Her blood tests showed a haemoglobin of 99 grams per litre (g/L) (normal range 130-180), white cell count of 11.48×10^9 per litre (/L) (4-11), platelet count 199×10^9 /L (140-400), mean cell volume of 74.5 fL (82-100). She had normal renal function. Her prothrombin time was 17.0 seconds (12.0 - 15.0),

activated partial thromboplastin time 30.8 seconds (24.0 - 35.0) and fibrinogen count 6.1 g/L (1.8 - 4.5). C reactive protein levels (CRP) levels were 99mg/L (<5). Her liver functions tests were bilirubin 34 umol/L (<21), alkaline phosphatase 179 U/L (30-130), alanine transferase 25 U/L (<40), total protein 68g/L (60-80) and albumin 34g/L (25-50). Her D dimer levels were 0.45 mg/L (<0.50).

Peripheral blood cultures were taken.

Her flu swab was negative and her chest radiograph, Figure 1, showed consolidation in her left upper lobe as well as probable bilateral upper lobe shadowing. Her electrocardiogram, Figure 2, showed a narrow complex tachycardia at 158 with altered P wave morphology, consistent with an atrial tachycardia.

Arterial blood gas analysis on air showed a normal pH and carbon dioxide but a low arterial partial pressure of oxygen at 8.5 Kilopascals (10.7 – 13.3 kPa).

She was seen in Accident and Emergency by an acute medicine registrar who reviewed all of the above and performed a point-of-care cardiac ultrasound (POCUS). No images are available from that test but it showed a dilated right ventricle with probable septal bowing.

Due to the presentation with an atrial tachycardia, which was slightly out of keeping with a response to an infection, the registrar sent off thyroid function tests as he had previously come across a similar presentation and had diagnosed hyperthyroidism.

Differential Diagnosis

Hypoxia it is due to a mismatch between ventilation and perfusion. Her chest radiograph showed consolidation and her symptoms and observations point to a pneumonia with a systemic inflammatory response. Differential diagnoses of consolidation on a chest radiograph include infective pneumonias, poorly differentiated cancers, cavitatory lesions associated with autoimmune conditions or pulmonary haemorrhage.

She had low haemoglobin levels as well as a low mean corpuscular volume. This points to iron deficiency. Haematinic levels should be checked.

Pleuritic pain is often associated with respiratory infections but also with pulmonary emboli (PE). The POCUS demonstrating right ventricular dilatation and dysfunction suggests that the differential must include PE, (despite a negative D dimer) as her Wells score was 4.5. This put her in a moderate risk group which carries a 16.2% chance of PE in an emergency population.

Atrial tachyarrhythmias can occur in people with structurally normal hearts and can be triggered by infection, drugs, alcohol, electrolyte disturbances or metabolic disorders such as hyperthyroidism. However, occult underlying structural heart disease such as dilated or hypertrophic cardiomyopathy,

valvular problems (e.g. mitral valve prolapse), congenital heart disease (e.g. atrial septal defect) or rarer conditions such as arrhythmogenic right ventricular cardiomyopathy (ARVC) should be considered, as these can all occur in younger patients.

Treatment

Intravenous fluids, broad spectrum antibiotics (piperacillin-tazobactam) and oxygen to keep saturations between 90 and 94% were prescribed. Full dose tinzaparin was administered subcutaneously and a computed tomography pulmonary angiogram (CTPA) was ordered.

Figures 3-5 show slices of the CTPA. Images were degraded by artefact but there were no large pulmonary emboli. There was no reflux of contrast in the hepatic veins, and no bowing of the intraventricular septum. There were bilateral moderate volume pleural effusions (Figure 3), with dense consolidation of the left lower lobe (Figure 4). There was also a diffusely bulky thyroid noted (Figure 5).

Her thyroid function tests came back as showing a free (T4) thyroxine of 46 pmol/L (10-22) , a triiodothyronine (T3) of 33 pmol/L (3.1-6.8), Thyroid stimulating hormone (TSH) levels of <0.01 mIU/L (0.3- 4.5).

A formal transthoracic echocardiogram was performed, which showed normal left ventricular size and systolic function. The right ventricle was dilated with preserved function. Paradoxical interventricular septal motion (or LV "D-shaping") was seen in systole due to right ventricular volume overload. There was mild right atrial dilation and mild tricuspid regurgitation. The interatrial septum appeared to bulge from right to left but there was no evidence of trans-septal flow. There was a thin layer of pericardial fluid seen around the heart but no evidence of haemodynamic compromise. The systolic pulmonary artery pressure was 24mmHg added onto right atrial pressure. (Figure 5 and Video 1)

Her N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was 2908 ng/L - a level of more than 2000 is strongly associated with heart failure and carries prognostic implications.

Her serum ferritin was 15 ug/L (12 – 250). B12 and folate levels were normal. Coeliac serology was negative.

An endocrinology consult was sought and she was started on propranolol 40mg four times a day as well as carbimazole 40mg once a day. There was no eye or skin disease on targeted examination. A pregnancy test was negative.

Outcome And Follow-up

Within a few hours with fluids, antibiotics and oxygen, the patient's symptoms had improved considerably. With the addition of the beta blocker and carbimazole on the day of admission, her heart

rate gradually slowed down and she converted to a normal sinus rhythm later the same day. Had her arrhythmia persisted, an adenosine challenge could have been performed to differentiate focal atrial tachycardia from atrial flutter or a re-entrant SVT, to allow more targeted antiarrhythmic therapy or consideration of eventual electrophysiology studies with ablation if required.

On day 3, her observations were completely normal and she felt ready to go home. She was prescribed a course of oral amoxicillin 500mg three times a day for five days and ferrous sulphate 200mg three times a day. Blood cultures were negative.

She was reviewed in a respiratory outpatient clinic within 2 weeks and all her symptoms had resolved. Bilateral thoracic ultrasound showed that her effusions had completely resolved. She was referred to the smoking cessation clinic.

She was reviewed in endocrinology a week later. Further results were available for review: TSH receptor antibodies were 57.7 IU/L (1.0 - 1.8) and thyroid peroxidase (TPO) antibody levels were 129 kU/L (0.0 - 34.0).

A diagnosis of Grave's disease was made. T3 levels were 6.5, T4 levels were 4.9 and TSH levels were <0.01. She had a normal resting heart rate and her propranolol was reduced to 40mg once a day. Carbimazole was continued.

Further review four weeks later revealed that she had developed a neutropenia. Her carbimazole was stopped and propylthiouracil 100mg twice a day for 6 weeks was started. A goitre was also noted as before, but no eye or skin disease.

A cardiology consult was sought. It was felt that the initial clinical and radiological picture, with evidence of new pleural effusions, RV dilatation and volume overload were consistent with high-output cardiac failure, driven by hyperthyroidism. An outpatient cardiac magnetic resonance (CMR) scan was requested to evaluate for any structural abnormalities that might suggest the echocardiographic findings preceded the acute illness. It was particularly important to look for an atrial septal defect, which can be associated with atrial arrhythmia and are easily missed by echocardiography) and ARVC, which although rare can cause life-threatening ventricular arrhythmia. Both might appear just as a dilated right heart on echo, especially in the absence of PE, significant chronic lung disease, or left sided heart disease.

The CMR demonstrated a structurally normal heart, with normal indexed sizes of all chambers, normal ventricular wall thickness and no evidence of valvular pathology. The earlier RV dilatation and LV D-shaping had entirely resolved (Videos 2 and 3), suggesting that the right ventricle was no longer volume overloaded, consistent with resolution of the acute illness. Aortic and pulmonary valve flow mapping showed no evidence of left-right shunting (and thus excluding a haemodynamically significant ASD), and dedicated sequences of the RV free wall did not meet any Task Force criteria for ARVC such as focal dyskinesia or aneurysm. Tissue characterisation using late gadolinium enhancement, T1 and T2* mapping showed no evidence of infarction, diffuse fibrosis or suggestion of other underlying

cardiomyopathy (Figure 6). Interestingly, volumetric analysis demonstrated persistently hyperdynamic ventricles (LV ejection fraction 71%, RV EF 75%), which in a resting patient might suggest on-going hyperthyroid state in convalescence.

Discussion

In the human embryo, the thyroid gland develops at about 3-4 weeks gestation from the pharyngeal floor. It then migrates to the front of the neck. It consists of two connected lobes and the lower two thirds of the lobes are joined by connective tissue called the isthmus. The thyroid gland secretes three hormones: two thyroid hormones – triiodothyronine (T3) and thyroxine (T4) as well as a peptide hormone called calcitonin. [1]

In children, T3 and T4 are crucial for growth and development, and in adults, they are responsible for regulation of the intrinsic metabolic rate and protein synthesis. T3 and T4 secretion is regulated by thyroid-stimulating hormone (TSH), which is secreted from the anterior pituitary gland. TSH is regulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus. [1]

Hyperthyroidism is the overproduction of thyroid hormones. It has many causes: multinodular goitre, toxic adenomas, thyroiditis, excessive ingestion of iodine, pituitary adenomas and Graves' disease. The overall prevalence of hyperthyroidism is approximately 1.3 percent and increases to 4 to 5 percent in older women. The male to female prevalence ratio is 1:5 and hyperthyroidism is also more prevalent in smokers. [2]

Grave's disease causes up to 80% of hyperthyroidism. It is an autoimmune condition where the main autoantigen is the thyroid-stimulating hormone (TSH) receptor (TSHR). Lymphocytes from the thyroid tissue of patients affected by Grave's disease secrete thyroid autoantibodies, including thyrotropin receptor antibodies (TRAb). The presence of TRAb is very sensitive and specific for Grave's disease and is used to determine therapy. [3,4]. Grave's disease is also associated with other autoimmune conditions such as pernicious anaemia and immune thrombocytopenia. [1-4]

Thyrotoxicosis is the clinical syndrome resulting from hyperthyroidism and often the terms are used interchangeably. The clinical manifestations of Grave's disease are those of hyperthyroidism, a diffuse goitre as well specific orbitopathy and dermopathy. The pathogenesis, diagnosis and treatment of the latter two conditions are beyond the scope of this article and our patient did not have any of those. [1-4]

Clinical features of hyperthyroidism include: warm skin, lid lag, breathlessness due to increased ventilatory drive; respiratory muscle weakness and pulmonary hypertension, cachexia due to an increased metabolic rate, osteoporosis due to thyroid hormones stimulating bone resorption, normochromic, normocytic anaemia due to an increase in plasma volume, behavioural and personality changes such as psychosis, agitation, and depression and lastly cardiovascular problems which we will describe further. [5]

The cardiotoxic effects of hyperthyroidism are well described with an estimated epidemiology of between 12% to 68%. Thyrotoxic heart failure (THF) is due to myocardial damage due to the toxicity of abundant serum free T3 and T4. This causes altered energy synthesis by cardiomyocytes (oxidative phosphorylation glycolysis), impaired intracellular metabolism and protein synthesis) and defective myofibril contractile function [6]. Typical manifestations include left ventricular hypertrophy and systolic dysfunction (up to 47%), sinus or atrial tachycardias (up to 90%), dilated cardiomyopathy (estimated at 1%), pulmonary hypertension (29% in subclinical thyrotoxicosis and 39.6% in overt thyrotoxicosis) and diastolic dysfunction. [7] LV systolic dysfunction is reversible with treatment in around two third of patients. [8]

There are 3 recognised stages to THF: 1. Hyperkinetic phase with preserved ventricular function ("high output heart failure"), 2. Normo-kinetic phase in which there is reversible myocardial hypertrophy and diastolic dysfunction (heart failure with preserved ejection fraction or HFpEF) and 3. The hypokinetic stage characterized by systolic dysfunction and cardiac chamber dilatation (heart failure with reduced ejection fraction or HFrEF). THF is more common in elderly patients with other cardiovascular co-morbidities but younger patients without cardiovascular pathology can high output failure with myocardial hyper-contractility, as did our patient. This subgroup may still go on to develop HFrEF in a dilated cardiomyopathy phenotype particular in untreated chronic severe thyrotoxicosis. HFrEF is associated with significantly worse prognosis than HFpEF [9], although this could be less generalisable to THF where there is a clear reversible cause. Decompensation of heart failure can occur with intercurrent illness such as infections.

We surmise that our patient already had a propensity to develop thyroid disease (as she had pernicious anaemia already) and had been hyperthyroid for some time. The pneumonia caused her decompensation and admission to hospital. Fortunately, her cardiac involvement was in the hyperdynamic or high-output phase and her cardiac function returned to normal with early treatment.

Treatment of THF is well established. [7,10,11] The normalisation of the circulating thyroid hormones can take some time and thus any symptoms and signs of THF must be managed in the interim. In patients with THF, with or without structural heart disease, beta blockers such as propranolol, bisoprolol or metoprolol are recommended until a euthyroid state has been achieved. Propranolol is usually used first line as it is non-cardioselective and inhibits peripheral conversion of T4 to T3 as well as its cardiac effects.[12] Beta blockers lower heart rate and reduce contractility (negative chronotropic and inotropic effects), but can also directly treat arrhythmias by increase AV node refractory period and reducing excitability of ectopic foci. They have significant prognostic benefit in LV systolic dysfunction (HFrEF). [13] Diuretics can help in overloaded states [10,13]. Our patient clinically improved on propranolol, the dose of which was slowly reduced over time.

Suppression of thyroid hormones can be done with anti-thyroid drugs, radioactive iodine or thyroidectomy. Carbimazole is a pro-drug and is converted to methimazole after absorption. Methimazole prevents thyroid peroxidase enzyme from iodinating and coupling of tyrosine residues on thyroglobulin to

reduce the production of T3 and T4. Carbimazole is associated with significant side effects most notably bone marrow suppression leading to neutropenia and agranulocytosis. Should this happen, patients are normally swapped onto propylthiouracil which inhibits the formation of T3 and T4 by blocking the enzyme thyroperoxidase.[10] This happened with our patient.

Her reassuring convalescent CMR and the resolution of her pleural effusions would suggest that all of her initial clinical and echocardiographic features of heart failure were due to acute thyroid-related heart dysfunction and not underlying cardiac disease. The persistence of hyperdynamic ventricular function on CMR at two months suggests that thyroid control is not yet fully established.

Radioactive iodine induces hypothyroidism and has high success rates but imposes significant limitations on patients. Patients who receive radioiodine can expose their home and household contacts via saliva, urine, or radiation from their body. They should avoid sharing cups or utensils, sleeping in the same bed with another adult, pregnant woman, infant, or child, sexual contact and close contact with children and pregnant women. Pregnancy should also be delayed for four to six months. [10] Our patient declined this because of her job and the fact that she could not isolate herself. She is now considering thyroidectomy as a definitive management option and continues under regular follow up.

Learning Points/take Home Messages

- Hyperthyroidism is the excessive production of thyroid hormones and thyrotoxicosis is the resulting clinical syndrome
- Point of care ultrasound (POCUS) in acute medical admissions can significantly alter the differential diagnosis and help diagnose cardiac dysfunction
- Thyrotoxicosis can cause heart failure and atrial tachyarrhythmias, most commonly atrial fibrillation.
- Initial treatment is a combination of beta blockers and anti-thyroid drugs, with improvement in cardiac function in the majority of

Declarations

Written consent was obtained

There was no funding for this research

There are no competing interests

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Supplemental Legends

Video 1: Echocardiogram: Apical Four-Chamber window demonstrating dilated RV with impaired systolic function, paradoxical septal motion, dilated RA and small pericardial effusion

Video 2: Cardiac MRI short-axis cine at the papillary muscle level demonstrating normal biventricular function with resolution of RV overload and normal septal motion.

Video 3: Cardiac MRI long-axis 4-chamber cine demonstrating normal chamber sizes with resolution of previous RV dilatation/impairment.

Patient's Perspective

I was initially very scared of being very breathless and could not understand that it was my thyroid that has caused me to go into heart failure and have pneumonia as well. I thought that these diseases were associated with old people. With treatment, I have started to feel better and now understand more about the disease. I am scared about any further treatment I might have and in case I want to have a baby. However, I trust my doctors to do what they think is right for me.

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Figures



Figure 1

Electrocardiogram showing narrow complex tachycardia at 158bpm with altered P wave morphology consistent with atrial tachycardia.

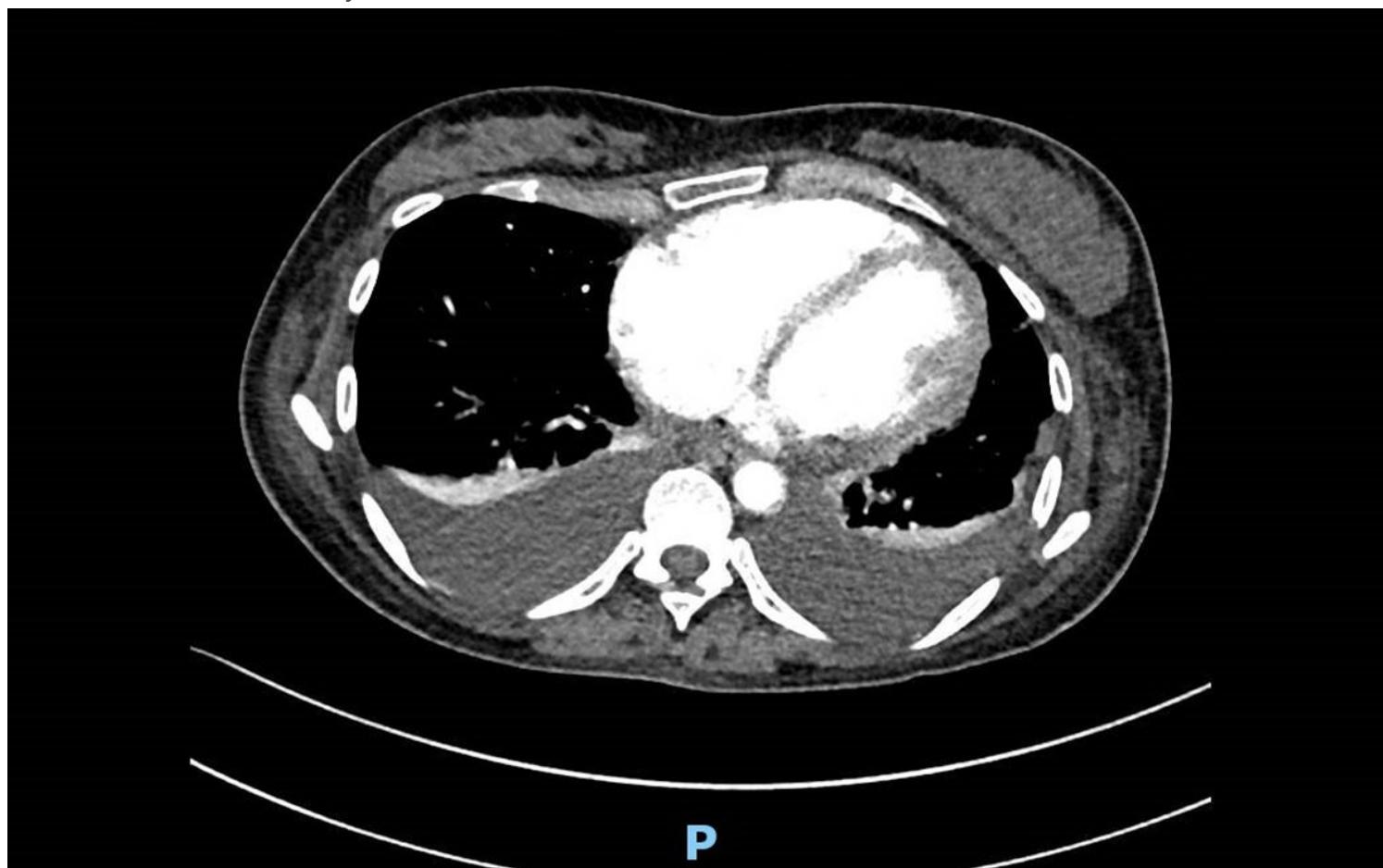


Figure 2

CT scan slice showing bilateral moderate volume pleural effusions



Figure 3

CT scan slice (lung windows) showing dense consolidation of the left lower lobe

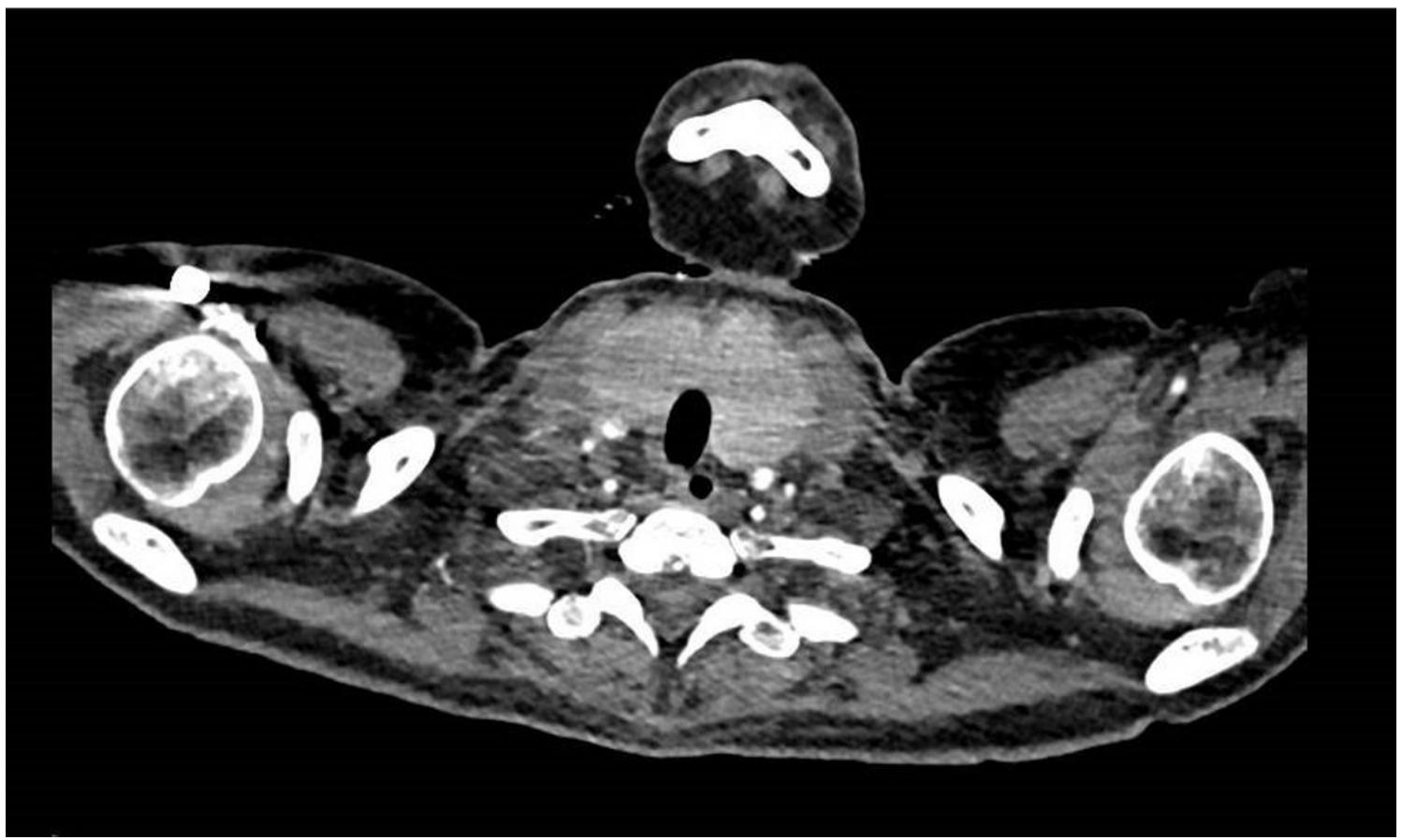


Figure 4

CT scan slice showing a diffusely bulky thyroid noted

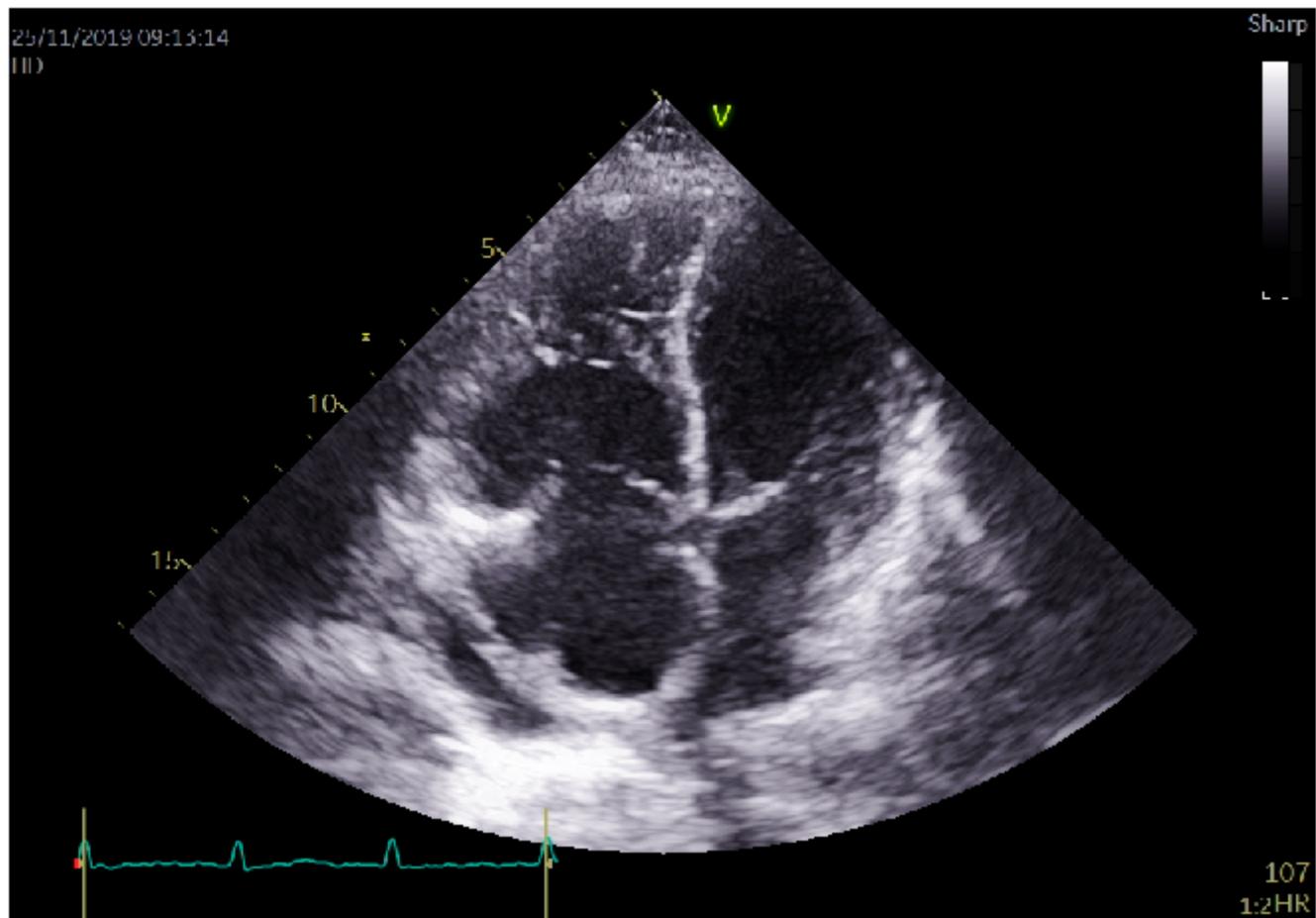


Figure 5

Echocardiogram: Parasternal short axis window showing paradoxical septal motion ("LV D-shaping") in systole as the volume overloaded RV compresses the LV.

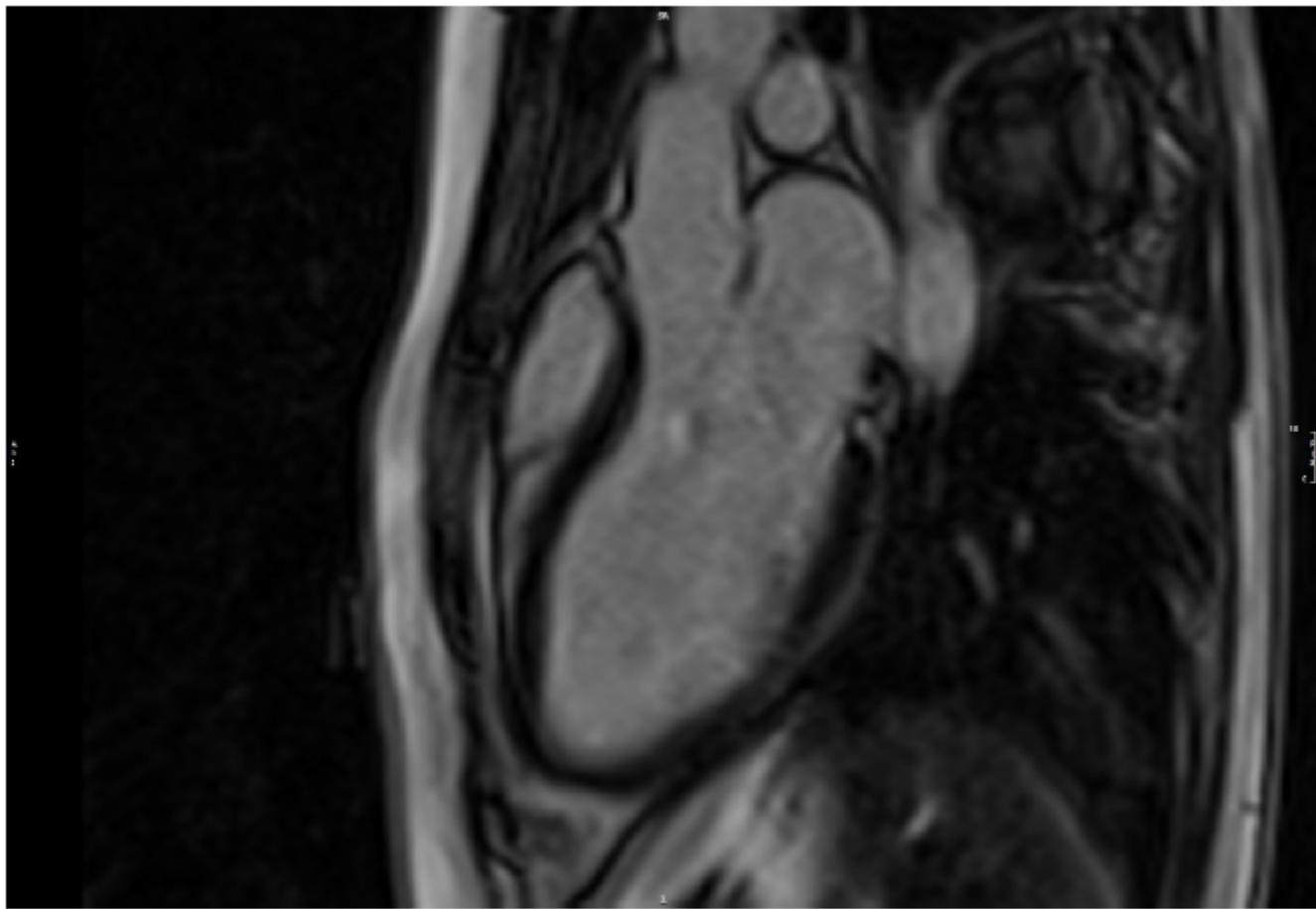


Figure 6

Cardiac MRI – apical long-axis view post-contrast demonstrating normal enhancement of the LV myocardium (black) without any late enhancement (white) that would suggest scar or fibrosis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Video3.avi](#)
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