Pancytopenia and nephrotic syndrome related to autoimmune hypothyroidism

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This case report highlights rare manifestations of hypothyroidism, its effects on the haematological and renal systems.

Case report

A 64-year-old woman presented to her general practitioner with a four-week history of progressive bilateral leg swelling, tiredness and dry skin. She had no significant past medical history. She was not taking any medication and there was no family history of thyroid or renal disorders.

On examination she had bilateral pitting oedema up to her knees, BP was 147/81 mmHg. Initial investigation showed heavy proteinuria (4+ on urinalysis), full blood count revealed pancytopenia Hb 10.2 g/dL (ref range 11.5–16) normocytic anaemia, WBC 2.9×109/L (ref range 4–11) and platelets 127×109/L (ref range 150–400); impaired renal function with serum creatinine of 129 µmol/L (ref range 70–100) and total serum cholesterol was 12.2 mmol/L. Serum B12, folate and ferritin were normal.

At this stage, the possibility of nephrotic syndrome was raised and she was referred to nephrology services. Further investigations revealed – normal serum complement levels and normal autoimmune profile (ANA, dsDNA, ANCA, Ro/SS – A, Ro/SS – B, Sm, RNP, Scl 70, Jo1). Her thyroid function was abnormal with TSH 182 miu/L (0.2–6.0) and free T4 – 2.3 pmol/L (10.0–25.0). She was referred to endocrinology for further management.

On examination, she appeared grossly hypothyroid with dry skin, typical hypothyroid facial features, hoarse voice, and delayed relaxation of deep tendon reflexes. Her thyroid peroxidase antibodies were elevated 347 iu/L (<100) confirming the diagnosis of autoimmune hypothyroidism. Her adrenal cortex, gastric parietal, mitochondrial, smooth muscle, liver/kidney microsomal antibodies were negative.

In April 2008, she was commenced on 50 µg of thyroxine o.d. and 2 weeks later the dose was increased to 100 µg o.d. Proteinuria resolved within a few weeks of thyroid hormone replacement and over the next five months, serum creatinine normalized, eGFR improved and the pancytopenia completely resolved (Table 1).

Discussion

In hypothyroidism, plasma volume and RBC mass are both diminished, and blood volume is decreased. Anaemia of a mild degree is commonly present, and the haemoglobin level may be as low as 8–9 g/dl. Characteristically, the anaemia of hypothyroidism is normochromic and normocytic. Less commonly it can be macrocytic or microcytic. In a report looking at 202 individuals with hypothyroidism, the overall incidence of anaemia as per criteria established by the World Health Organization was slightly less than 30%. The anaemia was macrocytic in 16 cases, microcytic in nine cases, and normocytic in 32 cases.[1]

It is important to note that anaemia can occur due to coincident vitamin B12, folate or iron deficiency. Microcytic hypochromic anaemia in hypothyroidism can be due to iron deficiency, in women secondary to menorrhagia, or in men due to decreased iron absorption especially in those with associated achlorhydria or associated coeliac disease, but may have no obvious cause.

Hypothyroidism *per se* can cause anaemia. The pathogenesis of the anaemia is not precisely understood but appears to reflect a physiologic adaptation to the decreased tissue oxygen requirements resulting from a decrease in the basal

Table 1
Laboratory results at diagnosis and during treatment with thyroid hormone

	March 2008	*April 2008*	*Thyroxine started*	*June 2008*	*August 2008*	*September 2008*	*December 2008*
Haemoglobin (11.5–16 g/dL)	10.4	10.2		10.6	11.4	11.6	
WBC (4–11 x 10^9/L)	2.86	3.02		3.42	4.02	5.42	
Platelet (150–400 x 10^9/L)	133	127		132	132	183	
Sodium (135–145 mmol/L)	141	139				140	
Potassium (3.5–5.0 mmol/L)	4.6	4.0				4.5	
Urea (2.1–8.0 mmol/L)	8.7	5.8				7.2	
Creatinine (70–100 μmol/L)	129	123				81	
eGFR (mL/min/1.73m^2)	38	41				78	
TSH (0.2–6.0 miu/L)		182		32	1.1		0.44
Free T4 (10–25 pmol/L)		2.3		14	21.5		21.1

metabolic rate. Plasma erythropoietin levels have been shown to be low.[2] This contrasts with the findings in most other cases of anaemia, in which plasma or urinary erythropoietin levels are increased as a result of tissue hypoxia. Results of ferrokinetic studies show decreased erythropoiesis, prolonged plasma iron clearance rate and decreased maximum Fe59 utilization by red blood cells suggesting that hypothyroidism per se affect cellular needs for oxygen and interfere with erythropoiesis. In some hypothyroid individuals with anaemia and normal serum iron, B12, and folate levels, an increase in haemoglobin was observed with thyroid hormone replacement alone.[2]

The anaemia of hypothyroidism is not correlated with the severity of the hypothyroidism and typically responds more slowly following thyroid hormone therapy compared to treatment of iron deficiency anaemia with iron therapy.[3]

White blood cells and platelets are usually unaffected in hypothyroidism. Pancytopenia due to marrow hypoplasia is reported in patients with myxoedema coma.[4] It has been suggested that an associated autoimmune reaction against bone marrow is the underlying cause.[5] Acton *et al.* have reported pancytopenia in a patient with hypopituitarism and autoimmune hypothyroidism which resolved following initiation of corticosteroid and thyroid replacement therapy.[6] We are not aware of any report of pancytopenia occurring in a patient with primary hypothyroidism alone without associated myxoedema coma or hypopituitarism.

Besides, pancytopenia, our patient was noted to have heavy proteinuria with no known renal problems. It is well-known that thyroid hormone is essential for adequate growth and development of the kidney and plays an important role in water and electrolyte homeostasis. Hypothyroidism can cause significant changes in kidney function with reduction in glomerular filtration rate and renal plasma flow, leading to reduced creatinine clearance and rise in serum creatinine.[7]

About 55% of patients with primary hypothyroidism are noted to have a slight increase in the serum creatinine levels[8] that is usually reversible upon correction of the hypothyroid state.[7,9] Renal involvement in autoimmune thyroiditis is not uncommon, usually manifesting as proteinuria, seen in 11–30% of cases.[10–12] The most common glomerular lesion among these reports based on renal biopsy findings is membranous glomerulonephritis.[13] The pathogenesis of glomerular disease and proteinuria in patients with autoimmune thyroiditis is not well understood. The major proposed mechanism focuses on deposition of immune complexes in glomerular basement membranes in conjunction with derangement in renal hemodynamic and architecture secondary to hypothyroidism.[13]

There may also be mild proteinuria, secondary to increased capillary transudation of proteins.[14] Treatment with thyroid hormone enhances renal function and improves glomerular filtration rate, thereby normalizing these changes.

Conclusion

In summary, we have described two rare complications of hypothyroidism: renal impairment and pancytopenia. Our patient showed complete recovery of renal function as well as pancytopenia within five months of thyroid hormone replacement. Hypothyroidism should be considered in patients with unexplained kidney disease as well as in unexplained pancytopenia.

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