East and North Hertfordshire NHS NHS Trust

# Severe hyperlipidaemia due to nephrotic syndrome in a diabetic patient.

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## Introduction

Secondary hyperlipidaemia often provides a clue to the underlying systemic disease.

Although common in patients with diabetes mellitus, one should think of other secondary causes if there is a poor response to HMG CoA reductase inhibitors in a diabetic patient with good glycaemic control.

Here we present a case report of severe hyperlipidaemia in a diabetic patient with hypoalbuminaemia and nephrotic range proteinuria.

## Background

A 68 year old man with known type II diabetes mellitus had normal serum lipids until 2012 when his total cholesterol more than doubled from 3.2mmol/l to 7.9mmol/l. He had never smoked and stopped drinking alcohol a decade before. He had no family history of premature coronary heart disease or dyslipidaemia.

His past medical history included atrial fibrillation on warfarin and well medicated subclinical hypothyroidism. He suffered a large MCA infarct with expressive dysphasia and right upper limb weakness in 2006, when he had a body mass index of 40.1kg/m$^2$ (currently 29kg/m$^2$).
At presentation in 2012 his medications included digoxin, metformin, vildagliptin and thyroxine 25mcg daily.

A year prior to presentation his total cholesterol was 3.2mmol/l, serum creatinine 65 umol/l and HbA1c 44mmol/mol. When his total cholesterol rose suddenly to 7.9mmol/l (low density lipoprotein (LDL) cholesterol 4.3mmol/l), he was commenced on simvastatin 40mg. Months later, he was seen by a community diabetes specialist nurse following referral by his general practitioner, as his HbA1c had risen to 60mmol/mol.

Despite a successful effort to improve his glycaemic control (HbA1c 54mmol/mol) and biochemical euthyroidism, his total cholesterol rose to 9.3mmol/l. This prompted a switch from simvastatin to rosuvastatin 10mg, with subsequent titration to 20mg/d, and the addition of ezetimibe when 40mg/d of rosuvastatin was not tolerated. Gliclazide was added to further improve his diabetic control, and a referral was made to the local secondary care lipid clinic (total serum cholesterol now 7.3mmol/l). It was noted there that he had in fact developed macroalbuminuria in 2011, his urine ACR having previously been below detection range. There had been a coincident fall in serum albumin from 48g/l in 2011 to <15g/l in 2014.

This prompted referral to the nephrology clinic where a renal biopsy was arranged and confirmed systemic AL amyloidosis – lambda type (light chain amyloidosis). He had a negative autoimmune, viral and myeloma screen.

Furthermore, SAP scintigraphy showed a large amyloid load within the liver, spleen and kidneys but no definite cardiac involvement by echocardiography, with a left ventricular ejection fraction of 62%. He had a normal whole body CT scan.
Under a haematologist, he had 6 cycles of VCD chemotherapy (velcade, cyclophosphamide and dexamethasone) which he tolerated reasonably well.

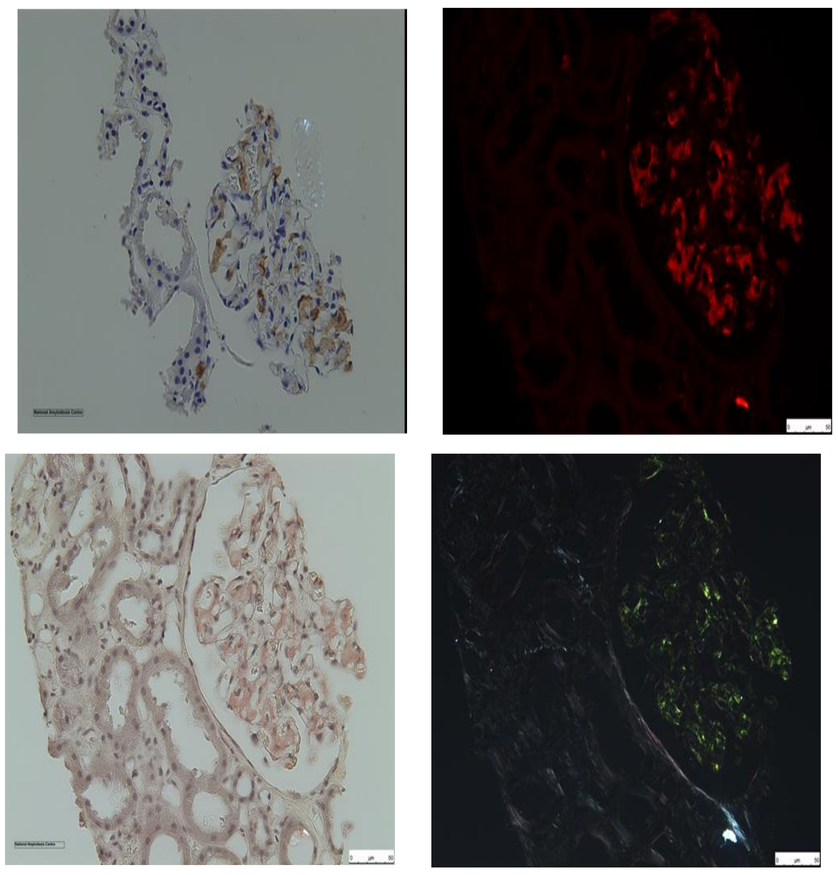

Figure 1 shows the diagnostic slides following renal biopsy with image (starting from the top left in a clockwise manner. 1) labelled with congo red ; 2) amyloid stained with congo red viewed under polarised light ; 3) amyloid stained under florescence light and 4) immunohistochemistry staining.

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## Learning points

- Think of secondary causes when dyslipidaemia is unresponsive to standard therapy in patients with well controlled diabetes mellitus.
- Always conduct urinalysis and serum albumin checks in diabetic patients and act upon abnormalities identified.
- Ensure that diabetes specialist nurses are aware of the typical lipid profile characteristic of diabetes, and when advice should be sought
- Consider nephrotic syndrome as a cause for dyslipidaemia
- Consider the possibility of amyloidosis in a patient found to have nephrotic syndrome.

## Abbreviations

AL: Light chain amyloidosis
HbA1C: Glycated haemoglobin
HDL-cholesterol: High-density lipoprotein cholesterol
HMG CO A reductase inhibitors: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.
LDL-cholesterol: Low-density lipoprotein cholesterol
MCA: Middle cerebral artery
SAP : serum amyloid P
VLDL-cholesterol: Very low-density lipoprotein cholesterol

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## Discussion

The clinical scenario above highlights the fact that dyslipidaemia, although common in diabetic patients, can be caused by other conditions. This case uncovered nephrotic syndrome due to amyloidosis as a cause of secondary dyslipidaemia unresponsive to statin therapy. Furthermore, proteinuria out of keeping with the duration and control of diabetes mellitus warrants a referral to a nephrologist with the aim of performing a biopsy so as to establish a diagnosis.

The causes of secondary hyperlipidaemia are numerous but they often demonstrate a distinctive lipid signature dependent on the underlying pathogenetic mechanisms (1). The lipid profile characteristic of diabetes mellitus comprises elevated circulating levels of triglycerides and decreased high density cholesterol (HDL-cholesterol) as well as an increase in the number of small, dense lipoprotein particles (2). An increase of 1mmol/L LDL-cholesterol is associated with a 1.57-fold increase in the risk of coronary heart disease in people with type 2 diabetes (3). Hyperlipidaemia is an integral feature of nephrotic syndrome, caused by an increased rate of lipoprotein synthesis as well as the defective clearance and catabolism of lipid particles. The characteristic lipid profile in nephrotic syndrome includes elevated total cholesterol, triglyceride, very-low-density lipoprotein (VLDL) and LDL cholesterol levels. There is also an abnormal distribution of HDL cholesterol subtypes (i.e. reduced HDL2 and elevated HDL3). Lipoprotein (a) may also be elevated(4).

There is a paucity of literature on hyperlipidaemia in amyloid nephropathy, but in a case report in the British Medical Journal in 1981, a 43 year old man with primary systemic amyloidosis had xanthomatous hyperlipidaemia preceding any detectable renal disease. Lipoprotein fractionation revealed elevated LDL and VLDL cholesterol. There was also reduced plasma HDL cholesterol (5).

In another case report a 48 year old man presented to a Japanese university hospital, with nephrotic syndrome due to primary systemic amyloidosis as a cause of secondary hyperlipidaemia. There was severe hypercholesterolaemia and hypertriglyceridaemia with high concentrations of VLDL -cholesterol and LDL - cholesterol. This lipoprotein pattern is also seen in myxoedema, familial hypercholesterolaemia and familial apolipoprotein E3 deficiency(6). In a more recent twelve year comprehensive retrospective profiling of 37 patients with renal amyloidosis in Brazil, only 6 patients were identified with hypercholesterolaemia (7).
The incidence of AL amyloidosis is about 8 per million per year and has been stable over the years (8).
The hypercholesterolaemia in amyloid nephropathy is caused by multiple mechanisms related to urinary loss of various proteins regulating cholesterol metabolism, and leading to impaired LDL clearance, increased cholesterol synthesis, diminished HDL-mediated reverse cholesterol transport, and diminished cholesterol (bile acid) secretion (10).

Treatment response of amyloid nephropathy is defined as more than a 50% decrease in 24-hour urinary protein excretion as it is associated with substantial benefit regardless of the type of therapy used (11).
The median survival after diagnosis of AL amyloidosis is 1 to 2 years and fewer than 5% of patients are alive 10 years after diagnosis (9). Renal amyloidosis is more likely to respond to intensive therapy than amyloid cardiomyopathy or two organ involvement (9).

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