

CASE REPORT

Lessons from treatment resistant hyperlipidaemia

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Abstract

A 68-year-old woman was referred to Lipid Clinic with sudden deterioration of previously well-controlled primary hyperlipidaemia. Investigations revealed nephrotic range proteinuria, leading to urgent renal biopsy and a diagnosis of amyloidosis. Chemotherapy was successful in stabilising renal function, reducing proteinuria and eliminating serum paraprotein. The resistant hyperlipidaemia subsequently resolved. Whilst hyperlipidaemia is pathognomonic of nephrotic syndrome, it is rarely the first characteristic identified by clinicians, often preceded by the identification of oedema or proteinuria. This case is an unusual example of a nephrotic syndrome presenting to Lipid Clinic as a resistant primary hyperlipidaemia, and highlights the importance of considering superimposed secondary causes of hyperlipidaemia in treatment resistant cases.

INTRODUCTION

The presence of a primary hyperlipidaemia due to inherited deficiencies in lipid metabolism does not preclude individuals from acquiring a co-existing secondary hyperlipidaemia. Nephrotic syndrome is one of many secondary causes of hyperlipidaemia. The compound effect of a secondary on primary hyperlipidaemia may lead to dangerous lipid levels that may precipitate pancreatitis, in addition to cardiovascular problems.

This report presents a case of sudden deterioration in previously stable primary hyperlipidaemia. The case aims to highlight how changes in control of hyperlipidaemia may indicate manifestation of new pathology rather than progression of a pre-existing condition

CASE REPORT

A 68-year-old woman was referred to Lipid clinic with unexplained deterioration of lipid control. Her total cholesterol and triglyceride levels were 15.4 and 14.3 mmol/L, respectively. Prior to this, lipids were significantly lower (total cholesterol from

2010, 2009 and 2005 was 6.8 mmol/L, 6.4 mmol/L and 5.9 mmol/L, respectively) controlled with Rosuvastatin 20 mg once daily. On discovery of this deterioration in lipid levels, medication was changed to Atorvastatin 40 mg once daily by her GP.

The peculiarity of this case was that the patient's hyperlipidaemia had previously been stable with statin therapy, suggestive of a secondary pathology.

The patient reported lethargy and bone pain for the past year. She had no history of diabetes, hypothyroidism or malabsorption. Her past medical history included hypertension, osteoporosis and obesity, and she abstained from alcohol and smoking. There was no family history of premature cardiovascular disease or pancreatitis, however, her three siblings were treated for hyperlipidaemia. She confirmed medication adherence. Other regular medications were, Valsartan, Furosemide, Alendronic Acid, AdCal D3, Fluoxetine and Cocodamol.

On examination, heart sounds were normal. There were bi-basal chest crackles and pitting oedema of the ankles. The abdomen was soft and non-tender. She had no cutaneous

Received: May 24, 2016. Revised: July 7, 2016. Accepted: August 8, 2016

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stigmata of hyperlipidaemia. Her blood pressure was 155/73 mmHg and BMI was 30.1 m²/kg.

Investigations showed urea 8.8 mmol/L, creatinine 76 µmol/L, eGFR 66 ml/min/1.73 m², fasting plasma glucose was 5.6 mmol/L and HbA1c and 6.1% (43.2 mmol/mol). Thyroid function tests revealed mildly raised TSH (8.4 IU/L). Liver function tests were unremarkable with the exception of hypoalbuminaemia (albumin 28 g/L) and haematology revealed a normocytic anaemia (MCV 88 fL, haemoglobin 102 g/L), folate 4.6 µg/L, low B12 (207 ng/L) and ferritin 329 µg/L.

Urine dipstick was negative for glucose, ketones and leucocytes, positive for nitrites, and 3+ positive for proteins. Protein creatinine ratio was 1431 mg/mmol, confirming nephrotic level proteinuria.

The presentation of therapy resistant hyperlipidaemia in the context of oedema, proteinuria and hypoalbuminaemia was consistent with that of nephrotic syndrome. Fenofibrate 160 mg was initiated due to the pronounced hypertriglyceridaemia. The patient was subsequently commenced on Levothyroxine 25 µg once daily to achieve euthyroid status and to ameliorate hypothyroidism as a contributing factor to hyperlipidaemia. Ezetimibe 10 mg was also initiated. Her TSH improved to 3.4 mIU/L, however, cholesterol remained elevated at 10.0 mmol/L and triglycerides at 5.7 mmol/L.

Further investigation showed a plasma cell dyscrasia secreting IgG λ paraprotein, with levels of 4.2 g/L. ANA was moderately elevated at 1:400, C-ANCA was negative and P-ANCA was indeterminately positive. Plasma viscosity was 1.91 cP. An urgent renal biopsy revealed Ig light chain λ amyloid deposits, confirming a diagnosis of Ig light chain (AL) amyloidosis. Serum amyloid P (SAP) scintigraphy showed moderate load of SAP within the liver, spleen, obscuring the kidneys.

The patient was referred for cyclophosphamide, bortezomib and dexamethasone chemotherapy. She remained monitored on triple lipid lowering therapy for mixed hyperlipidaemia.

Following six cycles of chemotherapy, serum paraprotein was undetectable, 24 h urinary protein 3.39 g/24 h, eGFR 54 ml/min/1.73 m² and albumin 36 g/L, showing a stabilisation of her condition. The patient's cholesterol reduced to 5.4 mmol/L, triglycerides to 4.3 mmol/L with HDL 1.1 mmol/L and LDL 2.4 mmol/L.

DISCUSSION

This case emphasises the necessity of considering nephrotic syndrome amongst differentials of hyperlipidaemia. Whilst nephrotic syndrome is a rare presentation of amyloidosis, with an incidence of approximately 30 per million per year [1], hyperlipidaemia may affect over 39% of the world population at any one time [2]. Although clinicians are primed to suspect nephrotic syndrome in presentations of proteinuria and oedema, due to its ubiquitous nature, hyperlipidaemia may not trigger such thought process. There is a case in the literature of nephrotic syndrome presenting as acute hyperlipidaemia, however this was discovered on presentation with pulmonary embolus due to hyper-coagulopathy [3]. The authors are not aware of another presentation where hyperlipidaemia was the sole presenting complaint, in which repeated assessments of hyperlipidaemia had led to lipid clinic referral. This represents a unique case to promote awareness of secondary hyperlipidaemias amongst healthcare professionals.

Hyperlipidaemia in nephrotic syndrome occurs largely due to impaired lipid catabolism and clearance, mediated by deficiency in hepatic LDL receptors [4], down-regulation of

cholesterol 7α-hydroxylase and impairment of lipoprotein and hepatic lipases. Compounding this, production of lipids is increased via up-regulation of HMG-CoA reductase [5]. The presence of hyperlipidaemia in nephrotic syndrome is between 80–99% with the degree of hyperlipidaemia related to syndrome severity [5]. Contrastingly, nephrotic syndrome is only present in a small number of cases of hyperlipidaemia [6].

Amyloidosis is characterised by the deposition of immune complexes in tissue. Primary systemic amyloidosis is rare, with incidence estimated at 8 per million per year [7]. Current opinion suggests that renal dysfunction in amyloidosis occurs through combination of physical disruption due to protein accumulation in the glomerulus, and direct cellular toxicity of amyloid deposits [8]. Disruption to the glomerular podocytes, fenestrated epithelium and basement membrane causes inability to filter by size and charge selectivity. Plasma proteins are therefore lost into the urine, leading to hypoalbuminaemia. Research has shown AL amyloid nephropathy to account for 10% of nephrotic syndrome presentations [9], however, despite its rarity, early diagnosis is crucial, as left untreated, it can be fatal [10].

This case aims to highlight the importance of considering nephrotic syndrome as a cause for hyperlipidaemia. Any change in previously well-controlled hyperlipidaemia may indicate new pathology. Due to the significant consequences of secondary hyperlipidaemias, these should be considered before presuming progression of a primary cause. Secondary pathologies include hypothyroidism, alcoholism, steroid use, diabetes, obesity and nephrotic syndrome amongst others. Severe hypertriglyceridaemia is a risk factor for acute pancreatitis, a potentially life threatening presentation. It is therefore essential to identify secondary hyperlipidaemias to ensure effective treatment. In this case, the nephrotic syndrome may also have contributed to subclinical hypothyroidism in an otherwise euthyroid individual. A further confound was the patient's BMI. Obesity contributes to hyperlipidaemia, however, is unlikely to cause this degree of hyperlipidaemia unless associated with apo E2 homozygosity.

This case highlights essential learning for practitioners less exposed to the secondary causes of hyperlipidaemia. Further, a diagnosis of a primary hyperlipidaemia should not preclude the possibility of a secondary hyperlipidaemia or its investigation. The authors recommend urine protein screening in all patients with unexplained or deteriorating hyperlipidaemia to exclude nephrotic syndrome.

ACKNOWLEDGEMENTS

The authors wish to thank the patient for their co-operation, information and allowing publication of this case report. Additionally the authors wish to acknowledge the help provided by Carole Jones throughout.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

No sources of funding.

ETHICAL APPROVAL

Approval was obtained from the patient. No other ethical approval was required.

CONSENT

Written informed consent was obtained directly from the patient discussed in this case study.

GUARANTOR

Elizabeth Parsons is the named guarantor for this article.

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