Two Types of Systemic Amyloidosis in a Single Patient

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The systemic amyloidoses are a group of rare diseases, in which extracellular deposition of a variety of proteins in an abnormal fibrillar confirmation results in life-threatening organ dysfunction.[1] Acquired and hereditary amyloidoses differ in their precursor proteins and predilection for specific organ involvement. Targeted biopsies or subcutaneous abdominal fat aspirate are used to confirm the presence of amyloid by Congo red staining viewed under polarized light, while immunohistochemistry and mass spectrometry can be used to characterize the amyloid fibril type. ^{123}I-labeled serum amyloid P component (SAP) scintigraphy and echocardiography or cardiac magnetic resonance are non-invasive means to map the distribution of amyloid deposits. Two types of fibril have been reported in a single organ,[2] and can complicate the same disease.[3] Recently, two types of amyloidosis have been described in a small case series.[4] Here, we report the first case of AA and AL amyloidosis in a single patient.

We report a woman of Sudanese origin who presented aged 31 with dysuria and haematuria. She was found to have an estimated Glomerular Filtration Rate of 38 ml/min and no proteinuria, and a renal biopsy demonstrated AA amyloid deposition. An I^{123} labelled SAP scan demonstrated a small amount of amyloid confined to the kidneys. She had no overt underlying inflammatory disease, an infectious diseases work up, including blood borne viruses, was negative and serial measurement of serum amyloid A protein showed no significant elevation with a median of 5 mg/L. Retrospective molecular analysis of the *MEFV* and *TNFRSF1A* genes, underlying Familial Mediterranean Fever and the Tumor Necrosis Factor Receptor Associated Periodic Syndrome, revealed the heterozygosity for *MEFV* E148Q and *TNFRSF1A* P46L common sequence variants of unknown significance. Interpretation of the significance polymorphisms in two fever genes remains contentious but given her persistently normal acute phase reactants, they were felt to be of no clinical relevance. Homozygosis for SAA1.1 allele of the *SAA1* gene is a recognised risk factor for

AA amyloidosis, but testing showed she was heterozygous. Management was blood pressure control only, and her inflammatory markers and renal function remained stable until she was lost to follow up 3 years later.

Thirteen years after her renal biopsy she represented in end stage renal failure with a history of weight loss, deranged liver function tests and marked easy bleeding. Further investigation demonstrated well controlled C reactive and serum amyloid A proteins, and an IgG lambda M-band with no serum free light chain bias. A bone marrow demonstrated 7% neoplastic plasma cells and was complicated by a retroperitoneal bleed. An SAP scan now showed a large amyloid load with amyloid deposition in the liver and spleen obscuring the kidneys [Figure]. Review of the bone marrow and a duodenal biopsy demonstrated amyloid deposition which was AL (lambda) type by both immunohistochemistry and proteomic analysis after laser dissection and mass spectroscopy. Review of the original biopsy confirmed AA type amyloid by both immunohistochemistry and proteomics. Six-cycle chemotherapy for AL amyloidosis was administered with complete clonal response. She remained on dialysis and died four years later of a cerebrovascular accident.

To the best of our knowledge, this is the first reported case of AA and AL amyloidosis developing consecutively in a single individual. The underlying inflammatory driver of her AA amyloidosis was never identified and given that she had migrated some years earlier from Africa, previous chronic infection that has resolved or responded to non-disclosed prior treatment was thought to be the most likely cause. Whether the subsequent development of AL amyloidosis was pure chance remains unclear. Theoretically, chronic inflammation/infection may drive generation of oligoclonal bands with the potential for monoclonal breakthrough. Whether her AA amyloid deposits played a role by providing a template for deposition of subsequent AL amyloidosis derived from an entirely separate

precursor protein is also unknown although this theoretically possible and has been shown in reverse in mice models.[5]

DECLARATIONS

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Data availability. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contributions: RP and HJL performed the research and wrote the manuscript; JAG performed the histology; NR performed the proteomic analysis; ADW, JDG, PNH and HJL treated the patient and contributed to writing the manuscript; and all authors approved the final version of the manuscript.

Abbreviations: SAP - serum amyloid P component.

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Figure. SAP scan image of our patient. The image shows the amyloid deposit in the liver and spleen obscuring the kidney.