Anasarca secondary to problems in three organs: one man with three diseases?

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A 50-year-old man presented with chronic diarrhoea and profound weight loss of 30 kg over 6 months. He reported passing watery loose stool up to seven times daily without obvious steatorrhoea. No significant travel history was noted, any risk factor of human immunodeficiency virus infection. Investigations including chest radiograph, abdominal ultrasonography, and stool culture for bacteria and parasites were unremarkable 2 months previously. His thyroid function was normal, as was his fasting glucose level.

He sought further medical advice because of worsening ankle swelling, by which time a gross oedematous state was noted with a distended jugular vein. His albumin level measured 14 g/l (normal range 36–48) and was consistent with protein-losing enteropathy. Oesophagastroduodenoscopy showed moderate gastritis and a normal duodenum, whereas colonoscopy did not suggest infection or inflammatory bowel disease.

Detailed cardiac examination confirmed an enlarged heart together with features of orthostatic hypotension and intractable heart failure. Electrocardiogram features reminiscent of myocardial infarction were noted (Figure 1), and an echocardiogram demonstrated marked left ventricular hypertrophy with minimal pericardial effusion.

The patient subsequently developed progressive renal insufficiency, accompanied by normal-sized kidneys and urinary loss of protein of up to 4.8 g daily. Of note, his urinalysis had been normal during the initial stage of the illness. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) were not detected. Urine protein electrophoresis showed features of glomerular proteinuria.

Question

- What is your diagnosis?

Correspondence and offprint requests to: Dr K. M. Chow,
Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong. Email: Chow_Kai_Ming@alumni.cuhk.net

Fig. 1. Electrocardiogram showing reduced QRS complex voltages and poor R-wave progression across the septum, reminiscent of myocardial infarction.
Multiple organ involvement with nephrotic-range proteinuria, cardiomyopathy and malabsorption led to a diagnostic evaluation focused on AL-amyloidosis. This patient’s electrocardiogram showed the cardinal features of cardiac amyloidosis, with reduced QRS complex voltages over standard leads, as well as poor R-wave progression across the septum on chest leads, as demonstrated in Figure 1. Peripheral blood film examination showed rouleaux formation, and bone marrow biopsy confirmed a monoclonal population of plasma cells of > 30%. Serum protein electrophoresis and immunofixation detected monoclonal IgA λ para-proteinaemia (8 g/l) with immune suppression of the physiological γ-globulins. Urine excretion of monoclonal IgA λ light chains and Bence-Jones proteinuria was confirmed by immunofixation. Furthermore, systemic amyloidosis associated with underlying multiple myeloma was confirmed by tissue diagnosis of random gastrointestinal tract biopsy, endomyocardial biopsy and fat pad biopsy, all of which were characterized by positive staining with Congo red stain and apple green birefringence under polarized light. Kidney involvement subsequently was documented by renal biopsy showing amyloid deposits in the mesangium, glomerular arterioles and larger vessel walls. Immunostaining for amyloid P component was positive in the same areas and negative for amyloid A protein, suggesting AL-amyloidosis. No abnormal plasma cells were identified in the interstitium. A moderate amount of tubular casts was noted, but they were not associated with giant cell reaction and were immunoreactive to both κ and λ light chains.

An interesting feature of this case was the manifestation of anasarca secondary to problems in three different organ systems, namely the gastrointestinal tract, kidneys and myocardium, all of them being related to one unifying diagnosis. Occam’s razor dictates that one should not increase, beyond what is necessary, the number of entities required to explain anything. To clinicians, this is a logical principle in our hypothesis-testing process. This case discussion highlights the importance of seeking parsimony—the simplest possible explanation of all findings—in the working diagnoses. AL-amyloidosis, also known as immunoglobulin light chain and primary amyloidosis, represents a systemic disease with classical multiple organ involvement [1]. Presumably, an underlying disorder of monoclonal plasma cell dyscrasia produces clonal light chain or fragment, which in turn forms a β-pleated sheet protofibril that ultimately polymerizes into the amyloid fibril. Fibril protein accumulation and deposition at various sites, the most common site being kidney, lead to organ dysfunction [1–3]. Whilst kidney involvement heralds the clinical manifestation of AL-amyloidosis most frequently [2,3], a subgroup of patients present predominantly with gastrointestinal symptoms and evidence of malabsorption syndrome [4,5], as was the case in our patient. In other words, an original diagnosis of protein-losing enteropathy does not necessarily obviate the need to search for other concomitant causes of hypoalbuminaemia. Urinary and gastrointestinal protein loss in our patient resulted in diminished intravascular oncotic pressure, and thus fluid transudation into the extracellular space with subsequent anasarca.

The oedematous state was compounded further by another complication of cardiac amyloidosis, which refers to the deposition of amyloid in the myocardium. Replacement of functional myocardial tissue (and, less frequently, endocardium, valves and pericardium) with inert, stiff β-pleated amyloid fibrils gives rise to reduced systolic function, impaired relaxation and diastolic dysfunction [6]. Electrocardiography (Figure 1) demonstrated the common finding of low voltage in the chest and limb leads, as well as pseudo-infarct patterns [1,7]. Of note, the latter pattern may cause diagnostic confusion with atherosclerotic heart disease. Clinically, the presence of cardiac amyloidosis often manifests as significant and progressive cardiomyopathy, which causes reduced stroke volume and hypotension, and compromises renal blood flow. Apart from worsening peripheral oedema, the predominantly right heart failure in cardiac amyloidosis contributes to hypoalbuminaemia as a result of hepatic dysfunction. Hepatic dysfunction occurs because of ischaemia or congestion, thus interfering with albumin synthesis [8]. Alternatively, hypoalbuminaemia might be related to intestinal congestion secondary to congestive heart failure, causing decreased protein absorption.

It is also notable in this case that the λ monoclonal light chains in the serum and urine did not produce a spike detectable by electrophoresis alone. As is often the case, the non-selective proteinuria in AL-amyloidosis can ‘bury’ the small amounts of excreted monoclonal light chains, which can only be recognized by antibody detection assays such as immunofixation electrophoresis or immunoelectrophoresis [2]. All patients with nephrotic-range proteinuria or clinical suspicion of AL-amyloidosis should therefore undergo immunofixation of serum and urine instead of electrophoresis.

In general, the diagnosis of amyloidosis is often not made until after the point of advanced and irreversible organ damage. The unifying diagnosis for the anasarca manifestation in our case, for instance, was only made when three different organ systems were involved. As the mortality of AL-amyloidosis is related to the number of organ systems involved, caution needs to be exercised by physicians in order to diagnose this progressive disease at an early stage, before multiorgan involvement limits our ability to treat [1,2]. Although renal amyloid accounts for <3% of renal biopsy specimens [9], renal physicians should pay special attention to this disorder (albeit rare) because kidney dysfunction is the presenting problem in one-third to one-half of all cases with amyloid [2].

Conflict of interest statement. None declared.
References


Grace Lai-Hung Wong
Kai Ming Chow
Angela Yee-Moon Wang
Philip Kam-Tao Li
Department of Medicine and Therapeutics,
Prince of Wales Hospital,
The Chinese University of Hong Kong,
Shatin, Hong Kong,
China