Disease classification: a pitfall of the ERA/EDTA registry?

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Introduction

Monoclonal proliferations of the B-cell lineage, often referred to as plasma cell dyscrasias or plasma cell disorders, are characterized by abnormal, uncontrolled expansion of a single clone of B cells at different maturation stages, with a variable degree of differentiation to immunoglobulin (Ig)-secreting plasma cells. They are thus usually associated with the production and secretion in blood of a monoclonal Ig or a fragment thereof. An ominous consequence of the secretion of monoclonal Ig products is their deposition in tissues, particularly in the kidney. These proteinaceous deposits can take the form of casts (in multiple myeloma cast nephropathy), crystals (in plasma cell disorder-associated Fanconi syndrome), fibrils (in light-chain and exceptional heavy-chain amyloidosis) or granular precipitates (in monoclonal immunoglobulin deposition disease). In a large proportion of patients, major clinical manifestations and mortality are related to visceral Ig deposition rather than to expansion of the B-cell clone. Indeed, except for multiple myeloma cast nephropathy, which is generally associated with a malignancy with a large tumour mass, Ig precipitation or deposition diseases frequently occur in the course of a benign B-cell proliferation or of a low-grade multiple myeloma.

Multiple myeloma is suggested to be one of the most common malignancies causing end-stage renal disease (ESRD), apart from neoplastic obstruction of the urinary tract. Until the 1980s, multiple myeloma-induced renal failure was associated with a very poor prognosis [1], and the question of the usefulness of dialysis had even been raised [2]. In recent years, both a better understanding of the triggering factors of acute renal failure and improvement of chemotherapy have prompted a reconsideration of the prognosis of acute kidney injury in multiple myeloma. In the majority of patients, renal function improves after correction of precipitating factors causing renal failure, namely hypercalcaemia, dehydration, infection and discontinuation of nephrotoxic drugs. However, a significant proportion of the patients who do not recover will require long-term renal replacement therapy, and uncertainties remain as to the outcome of those patients.

In this issue of Nephrology, Dialysis and Transplantation, Tsakiris and colleagues have attempted to address this question by using the ERA–EDTA Registry [3]. There is only one previous report from the United States Renal Data System (USRDS) that described characteristics and outcome of multiple myeloma patients in a national sample of patients with ESRD [4]. In both registries, the terms ‘multiple myeloma’ and ‘light-chain associated nephropathy’ (USRDS) or ‘light-chain deposition disease’ (LCDD) (ERA–EDTA Registry PRD code 82) are considered together although these terms designate completely different entities. In the ERA–EDTA Registry, there are separate PRD codes for amyloid (code 83) and Waldenström’s disease (code 78).

Tsakiris and colleagues [3] conclude that the incidence of renal replacement therapy for ESRD due to multiple...
myeloma and LCDD has increased over the past 20 years in Europe, and that the median patient survival on renal replacement therapy for multiple myeloma and LCDD was >4-fold shorter in those patients (0.91 years) than in non-multiple myeloma patients (4.46 years). Therefore, it is of paramount importance to address three questions: (i) Does the registry code 82 cover all complications of multiple myeloma? (ii) Is it legitimate to associate multiple myeloma and LCDD under the same code? (iii) If not, what should be done?

Renal complications of multiple myeloma: amyloidosis also!

Renal damage characterized by large protein casts surrounded by multi-nucleated giant cells within distal tubules was identified in the early 1900s and termed ‘myeloma kidney’. This term, however, should be abandoned because cast nephropathy with acute renal failure may occasionally occur in conditions other than multiple myeloma [5] and because other patterns of renal injury were subsequently found in patients with multiple myeloma. The first of these was amyloidosis, in which tissue deposits are characterized by Congo red binding and fibrillar ultrastructure. The spectrum of renal diseases due to monoclonal Ig deposition in the setting of multiple myeloma has still expanded with the advent of routine staining of renal biopsy specimens with specific anti-κ and anti-λ light-chain antibodies, and of electron microscopy [6]. Table 1 presents a list of renal lesions associated with multiple myeloma, classified according to the kidney compartment prominently involved.

Amyloidosis, a major complication of multiple myeloma, is not covered by PRD code 82, while code 83 codes for ‘all’ types of amyloid. In my opinion, this is a significant pitfall of ERA–EDTA Registry classification. Firstly, multiple myeloma is a major cause of amyloid light-chain (AL) amyloidosis, in which the deposits are composed of Ig light chains. Amyloidosis is found at autopsy in ~10% of multiple myeloma patients, with amyloid deposits being the most frequent finding after myeloma cast nephropathy (30% of autopsy cases) [7]. Its prevalence in this autopsy series was twice as high as that of LCDD. In 229 patients from the Mayo Clinic with proven AL amyloidosis, 47 patients had a true myeloma [8]. Secondly, AL amyloidosis has more impact on survival in dialysis than any other type of dialysis including amyloid A (AA) amyloidosis [9], which may lead physicians not to undertake renal replacement therapy. The management of patients with AL amyloidosis on haemodialysis is often complicated by persistent hypotension, gastrointestinal haemorrhage, chronic diarrhoea and difficulties in the creation and maintenance of vascular access. Cardiac involvement is a major predictor of patient survival. The outcome for patients with AL amyloidosis on dialysis is still a matter of debate [10]. In a recent French study [9], including 19 patients with AL amyloidosis undergoing dialysis, the median survival was 26 months (extremes, one to 96 months), while in the Mayo Clinic’s series, the median survival from the start of dialysis was 10.4 months, with 20% of patients dying within the first month and only 12% having a 5-year survival [11]. Thirdly, the prognosis of patients with amyloidosis undergoing dialysis markedly depends on the nature of the precursor protein which influences the extent of amyloid deposition and particularly the severity of cardiac involvement [9]. Indeed, cardiac complications are a major cause of death in AL amyloidosis, whereas they are less common in AA amyloidosis and in hereditary forms of amyloidosis except for transthyretin amyloidosis. As a matter of fact, AL amyloidosis with renal involvement shows more similarities with LCDD than with the various forms of amyloidosis.
LCDD

LCDD is a systemic disease characterized by deposition of monoclonal light chains, usually of the κ isotype, along the basement membranes in most tissues [12]. Those deposits are frequently asymptomatic except in the kidney, with the renal manifestations often dominating the clinical presentation. The term ‘monoclonal immunoglobulin deposition disease’ (MIDD) should be preferred to LCDD because monoclonal heavy chains are associated with light chains in ~10% of patients, and in rare cases, the deposits only contain monotypic heavy chains defining ‘heavy chain deposition disease’. The most common underlying disease in MIDD is multiple myeloma which accounts for ~50% of MIDD [12]. Apart from myeloma, MIDD may complicate Waldenström's macroglobulinaemia, chronic lymphocytic leukaemia and nodal marginal zone lymphoma (Table 1). It often occurs in the absence of detectable malignant process, even after prolonged follow-up. In such ‘primary’ forms, a monoclonal bone marrow plasma cell population can be documented easily by immunofluorescence examination.

Proposals for an improved classification of plasma cell-related disorders in ERA–EDTA registry

As pointed out by Tsakiris and colleagues [3], the inclusion of multiple myeloma and LCDD under one PRD code constitutes the main limitation of their study. Multiple myeloma is a ‘haematologic’ disease which may cause a variety of renal complications while LCDD is a ‘renal’ disease that may be caused by benign or malignant (lympho)plasma cell proliferation, so that their association under the same code is illogical and misleading. In addition, the Registry also suffers from lack of information regarding the histology and haematologic criteria for the diagnosis of multiple myeloma.

Tsakiris and colleagues [3] seem to deplore that the broader term of ‘plasma cell disorders’ is not used by the ERA–EDTA Registry. However, I would not recommend to use that term because of the heterogeneity of these disorders. The classification should rather be based on the nature of renal lesions that each can be caused by several benign or malignant haematological disorders. Diagnosis of myeloma cast nephropathy can often be made on clinical grounds including rapid onset, triggering factors and low output of albuminuria (<1 g/day), while that of other entities usually requires a kidney biopsy.

My suggestion would be to use three different codes based on presumed or biopsy-proven histological lesions: (i) myeloma cast nephropathy; (ii) AL amyloidosis, MIDD and other (rare) plasma cell disorder-related glomerulopathies; (iii) non-AL amyloidosis. Such classification would allow a more accurate description of the incidence/prevalence and outcome of the renal complications of plasma cell disorders at the stage of renal replacement therapy.

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References


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