Table 1 | Mechanisms proposed for carfilzomibrelated renal injury

	Number of cases	*Any therapy tried*	*Biopsy*	*Reference #*
Pre-renal insult	2	*N*-acetyl-L-cysteine	None	2,3
Tumor lysis syndrome	1	No	None	4
Thrombotic microangiopathy	1 (in a post-stem cell transplant setting and relapsed myeloma)	Plasmapheresis	Yes	5

kidney biopsy information might be critical. Although, in correspondence with many hematologists treating myeloma, the renal injury reported by them is transient with a quick recovery. In the two cases we had reported from our institution, the renal injury was transient and behaved as a 'pre renal' insult.[2,3] In addition, in one of our cases, we showed that *N*-acetylcysteine (NAC) was protective in preventing carfilzomib-related renal injury when the patient was rechallenged with the chemotherapy agent. We postulate that NAC might be preventing a vasoconstriction-related renal injury.[3]

As mentioned in your review,[1] there is a very low incidence of Food and Drug Administration (FDA)-reported adverse renal events with carfilzomib. However, we feel this may be due to the transient nature of the injury with quick renal recovery, not necessitating much reporting to the FDA. Nephrologists and hematologists need to be cognizant of the renal toxicity associated with this drug even though it may be transient in most of the cases.

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The Authors Reply: We appreciate the information provided by Drs Jhaveri and Wanchoo regarding carfilzomib-related nephrotoxicity.[1] They describe four cases of nephrotoxicity of varied etiologies developing in the setting of carfilzomib therapy. Two are considered prerenal acute kidney injury (AKI)[2,3] postulated to be due to drug-induced afferent arteriolar vasoconstriction by the authors, one of which appeared to respond to the anti-oxidant *N*-acetylcysteine.[3] Kidney tissue was not obtained in either case to define the renal lesion associated with carfilzomib and it remains unclear why the rise in serum creatinine occurred (and did not return to baseline despite drug discontinuation). Urinary granular casts seen in one of the cases suggests drug-induced tubular injury. Another report does not support direct renal toxicity as AKI developed as a consequence of tumor lysis syndrome associated with effective drug therapy of the underlying malignancy.[4] The final case described by the authors is thrombotic microangiopathy (TMA) developing in a patient treated with carfilzomib for relapsed multiple myeloma in the setting of hematopoietic stem cell transplantation (HSCT).[5] The true relationship of drug nephrotoxicity is complicated by the presence of HSCT, which can be associated with TMA.[6] Ultimately, we agree that carfilzomib does have potential to cause kidney injury; however, currently available data are insufficient to definitively identify the renal lesion. Notwithstanding this limitation, clinicians must be aware of this drug's nephrotoxic potential and continue to report adverse renal events, including a tissue diagnosis when possible.

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Monoclonal gammopathy of renal significance: systemic involvement by benign condition

To the Editor: Recently, some authors defined the so-called monoclonal gammopathy of renal significance (MGRS),

characterized by the presence of plasma cell dyscrasia, with the main renal damage and discriminated from classic monoclonal gammopathy of uncertain significance (MGUS) by a less benign course.[1,2] We appreciate the very exhaustive review of Bridoux *et al.*,[3] in which they defined useful criteria to diagnose this entity, linking the development of MGRS with many hematological diseases. Contributing to this classification, we describe the interesting association between a controversial condition and renal impairment due to amyloid deposition, even without an evident plasma cell neoplastic clone. AL amyloidosis represents a frequent epiphenomenon of plasma cells dyscrasia (PCD), and their association has been extensively studied during past years.[4–7] Although systemic involvement is more likely linked with advanced diseases, like multiple myeloma (MM), conditions always considered as benign could give rise to such manifestations, with adequate latency periods, as described by Kourelis *et al.*[4] For this reason, and for an adequate management, careful diagnostic assessment of these entities is crucial, and the recent development of more sensitive tools had a key role in this field. This improvement allowed the evolution of such condition defined by Mian *et al.*[5] as idiopathic Bence-Jones proteinuria (iBJP), later revised by Dispenzieri *et al.*[6] with the aid of serum free light chain (FLC) detection systems. In this context, we recently evaluated the case of a 66-year-old woman affected by polymyalgia rheumatica who initially did not fulfill the criteria for any known hematological condition (abnormal FLC ratio, increased level of FLC, no monoclonal heavy chain, fewer than 10% monoclonal plasma cells in the bone marrow). Interestingly, urine analysis demonstrated positivity to Bence-Jones protein, a hallmark already described by various authors.[5,6] Suddenly, the patient developed proteinuria within the nephrotic range (3.5 g per 24 h) and underwent renal biopsy. Despite the extremely low level of λ-FLC (28.24 mg/l), the histological study revealed renal AL amyloidosis (Figures 1a and b). Finally, these deposits were typified by electron microscopy (Figures 1c and d) with immunogold labeling.[8] A subsequent bone marrow biopsy and electrophoresis confirmed the presence of monoclonal light chain component without morphological evidence of clonal plasma cells. Interestingly, bone marrow was focally replaced by the presence of metastatic carcinomatous cells from occult lobular breast carcinoma (Figure 1e). Moreover, the vessels' walls of the bone marrow and breast tissue, collected to perform cancer diagnosis, displayed positivity to Congo red stain (Figure 1f). The systemic involvement made our case partially divergent from the benign course of the entity described by previous series,[5,6] although those could be applied to our patient because of our current limitations in detecting low levels of clonal cells using immunohistochemistry and flow cytometry on bone marrow specimens.[9] It is interesting to underline the disproportion between the slight FLC component and the impressive systemic involvement by amyloid deposition, a phenomenon that could be differently interpreted. On one hand, there may be another pathophysiological process that promotes the development of disseminated amyloidosis, and we are actually unable to detect it; on the other hand, a MGUS with this kind of behavior may have a more aggressive course and a potential poor outcome. In this second hypothesis, a further update of the entity definition may be required, supported by other analog case reports. A multidisciplinary approach with different techniques (high sensitivity immunofluorescence and specific immunogold electron microscopy) was also used to typify amyloidosis, highlighting the difficulty in solving these kinds of diagnostic issues. Furthermore, the clinical features of our disseminated amyloidosis were in agreement with a previous series in which such occult proliferations evoked exaggerated and unexpected

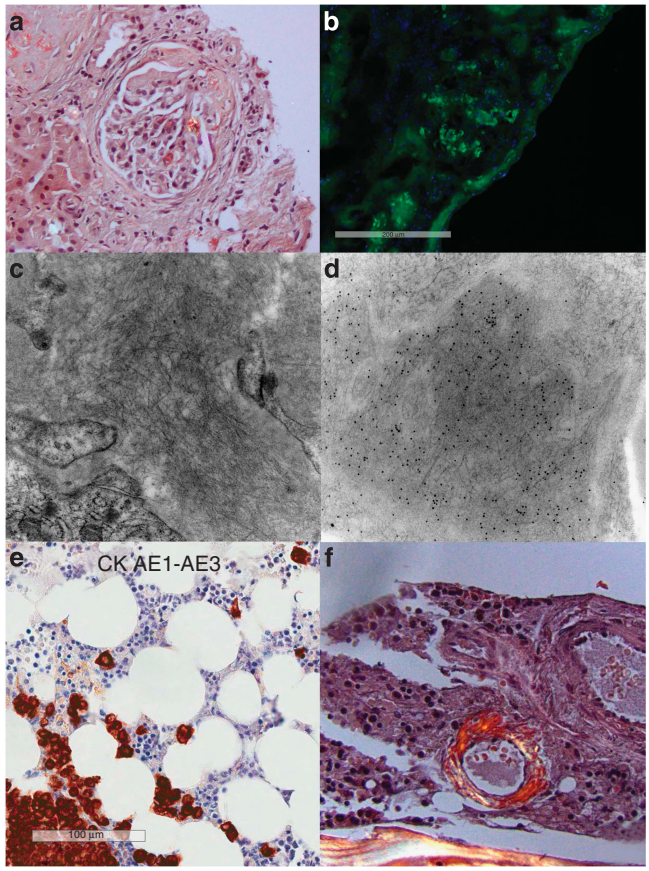

Figure 1 | (a) Segmental patchy deposition of amorphous eosinophilic material in mesangial areas with positivity to Congo red staining (note typical green-apple birefringence in polarized light, original magnification ×20). (**b**) Direct immunofluorescence on fresh-frozen 5 micron-thick sections revealed a questionable positivity to immunoglobulin λ-chain (×20 magnification). (**c**) Electron microscopy confirmed the presence of amyloidosis, with classic fibrillary deposition on mesangial areas (10 nm diameter, ×250 magnification). (**d**) Immunogold labeling confirmed the AL-type of amyloidosis (negative for k and SAP protein, ×300 magnification). (**e**) Bone marrow biopsy showed focal nodular aggregates of metastatic carcinomatous cells (positive for CK AE1-AE3, ×20 magnification and estrogen receptor, data not shown) from occult breast carcinoma. Plasma cells were mature (around 6% of the total cellularity) and without evidence of clonal restriction. (**f**) Congo red stain also revealed the slight deposition of amyloid in bone marrow vessels (×20 magnification) and breast vessels (data not shown).

systemic consequences.[10] Moreover, in a first instance, the unusual association between breast cancer and amyloid deposition was suggestive of a serum amyloid A–type amyloidosis, a phenomenon already reported in literature,[11] and then the positivity to λ antisera in immunofluorescence represented for us a surprisingly finding. Finally, our case was also particularly intriguing due to the possible link between renal and hematological disorders. In this context, our experience may add a further condition to Bridoux classification,[3] improving clinical management of monoclonal-related renal diseases.

DISCLOSURE
The authors declared no competing interest.

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The Authors Reply: We thank L'Imperio *et al.*[1] for their interest in our review on monoclonal gammopathy of renal significance (MGRS). They describe a patient diagnosed with 'disseminated' immunoglobulin light chain (AL) amyloidosis, without evidence of a symptomatic myeloma. In our opinion, this case is an excellent example of MGRS, emphasizing the importance of kidney biopsy and accurate typing of deposits for diagnosis. In MGRS, the pattern of renal lesions does not depend on the tumor mass, but rather on the physicochemical properties of the variable domain of pathogenic monoclonal immunoglobulins.[2] This case is actually quite typical of AL amyloidosis as 60% of these patients have $<10\%$ plasma cells in the bone marrow at diagnosis.[3] Moreover, in our experience with 202 biopsy-proven cases of renal AL amyloidosis, 74% had bone marrow amyloid, 80% had abnormal serum free light chain ratio, and 79% and 84% had a positive serum or urine immunofixation, respectively.[4] Despite that, systemic AL amyloidosis should not be considered benign as these patients progress to end-stage renal disease and even death if proper treatment is not initiated. The presence of amyloid in vessels of bone marrow and other organs is a common finding in systemic AL amyloidosis, and histological breast vascular involvement was likely only detected because of the unrelated breast cancer in this patient. Finally, we would like to stress the need of careful clinical assessment in MGRS disorders, especially those with frequent systemic extension, such as AL amyloidosis or light-chain deposition disease, to detect other organ involvement, particularly heart disease.

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