
Renal involvement in autoinflammatory diseases and inflammasome-mediated chronic kidney damage

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Received on November 27, 2017; accepted on December 7, 2017.

Clin Exp Rheumatol 2018; 36 (Suppl. 110): S54-S60.

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Key words: autoinflammatory diseases, chronic kidney disease, inflammasome, inflammation, interleukin-1, proteinuria, secondary amyloidosis

Funding: this paper is part of a supplemental issue supported by an unrestricted grant from Novartis Farma, Italy through a service agreement with Health Publishing & Services Srl. Health Publishing & Services Srl provide editorial assistance. Article Processing Charges were also funded by Novartis Farma, Italy.

Competing interests: L. Obici has received speaker's fees and travelling support from Novartis. R. Scarpioni has received speaker's fees from Novartis.

ABSTRACT

Unprovoked activation of innate immune pathways and increased secretion of interleukin (IL)-1 β and IL-18 are responsible for the protean clinical manifestations and the marked inflammatory response that characterise most hereditary autoinflammatory disorders. The kidney is a major target organ of this inflammatory process. The deposition of the acute-phase reactant serum amyloid A (SAA) as amyloid causes progressive glomerular and vascular damage and leads to organ failure. In this review we focus on the potential impact of hereditary autoinflammatory diseases on renal function, provide red flags that may guide the clinical suspicion of amyloid kidney damage and discuss the relevance of close renal monitoring for early diagnosis and prompt treatment. Moreover, NLRP3 inflammasome activation is increasingly recognised to play a key causative role in the pathogenesis of several chronic kidney diseases in which activation of caspase-1 and the proteolytic cleavage of IL-1 β and IL-18 into their biologically active forms mediate glomerular and tubulointerstitial damage. Although much of the knowledge about the role of the inflammasome in kidney injury has been mostly gathered in experimental models, inhibition of IL-1 is also becoming an attractive potential therapeutic target in a variety of chronic renal disorders with a substantial inflammatory component.

Introduction

Hereditary autoinflammatory diseases (AIDs) are disorders of the innate immune system characterised by unprovoked attacks of fever and systemic inflammation in the absence of autoantibodies and autoreactive T cells (1). The molecular mechanisms underlying AIDs relate to impaired intracellular danger signalling and/or aberrant in-

flammasome activation, leading to dysregulation of the inflammatory response and overproduction of proinflammatory cytokines, especially interleukin (IL)-1 β (2). Increased IL-1 β secretion is responsible for most of the systemic features of this group of disorders and for the persistent acute-phase response associated with them (3). The kidney is a major target organ of this inflammatory process. Kidney damage is mediated by the deposition of the acute-phase reactant serum amyloid A (SAA) as amyloid, which causes progressive glomerular and vascular damage and leads to organ failure. AA amyloidosis is therefore a serious complication of this group of disorders and represents a medical challenge with relevant unmet needs (4).

Major progress in understanding the molecular mechanisms that trigger hereditary AIDs has contributed to highlight the role of immune-mediated inflammation also in more prevalent, acquired conditions including diabetes, obesity, atherosclerosis, crystal-related diseases and neurodegenerative disorders (5, 6). In addition, aberrant renal danger signalling and innate immune activation have also been shown to contribute to the inflammatory process associated with many acute and chronic kidney disorders (7, 8). The inflammasomes, a family of large subcellular multiprotein complexes that sense cellular stress signals and trigger inflammatory responses, are emerging as key mediators of innate immune activation in these multifactorial conditions. In particular, a pivotal role is played by the NLRP3 inflammasome, whose activation is induced by diverse pathogens and host-derived signals of cellular damage [reviewed in (9, 10)] and results in proteolytic cleavage of caspase-1 into its biologically active form, which in turn mediates the production of IL-1 β and IL-18 pro-inflammatory cytokines (11).

In this review we focus on the multiple, intertwined mechanisms that link autoinflammation and kidney injury. On the one hand, AIDs may affect renal function through amyloid-mediated damage, on the other hand, increasing evidence indicates that NLRP3 inflammasome activation and IL-1 β -mediated vascular harm play a role in the pathogenesis of several chronic kidney diseases. This suggests that targeting these mechanisms may improve the outcome of several renal disorders with a substantial inflammatory component.

Autoinflammatory diseases and amyloid-mediated renal damage

Unprovoked activation of innate immune pathways and increased secretion of IL-1 β and IL-18 are responsible for the protean clinical manifestations and the marked inflammatory response that characterise most hereditary autoinflammatory disorders (11). A persistently or recurrently elevated concentration of the circulating acute-phase reactant SAA is therefore a hallmark of these diseases but also predisposes to the self-aggregation and extracellular deposition of this protein as insoluble amyloid fibrils in different tissues.

AA amyloidosis is one of the best characterised systemic forms of amyloid disease (12). AA amyloid tissue pathology and fibril composition have long been investigated in humans and animals (13), and seeding, accumulation and clearance of AA deposits have been shown in several experimental models (14-17). However, the molecular mechanisms underlying misfolding and aggregation of this protein into cross- β -sheet fibrillar deposits and the reasons for preferential accumulation in the renal glomeruli in humans are far from being clarified (13).

Whereas a persistently elevated concentration of SAA is a prerequisite for AA fibrillogenesis, its physiological role in acute and chronic tissue injury is not fully understood. However, evidence points to an evolutionary conserved function of this protein in promoting the mobilisation and recycling of cholesterol from damaged tissue for cell repair (18). Following secretion by hepatocytes, SAA rapidly binds through

its N-terminal domain to the surface of high-density lipoproteins (HDL) and, by displacing apolipoprotein A-I and other apolipoproteins, redirects them towards tissue macrophages, where it activates cholesterol efflux. The intrinsically disordered structure of SAA, that at near-physiological conditions spans multiple conformations, supports its ability to interact with multiple ligands, including lipids, cell receptors, and proteoglycans (19). Interactions with glycosaminoglycans and macrophages have been shown to promote both the dissociation of SAA from HDL (18, 20, 21) and its proteolytic remodelling by one or more as yet unidentified enzymes, releasing the N-terminal cleaved fragments predominantly spanning the first 76 amino acids that are ultimately found in AA amyloid fibrils. Interestingly, an association between AA fragment length, intensity of amyloid birefringence and pattern of renal deposition has been reported, suggesting that cleavage is a key and specific event that drives SAA fibrillogenesis and tissue pathology (13).

Clinically, AA amyloidosis presents in its early stages with a low-grade proteinuria that usually progressively worsens if the inflammatory stimulus persists or recurs over time, leading to nephrotic syndrome and ultimately renal failure. Advanced renal dysfunction at diagnosis and persistent elevation of SAA during follow-up are powerful risk factors for progression to end-stage renal disease (ESRD) and death (22). Recently, we reported that renal survival was independently predicted by proteinuria (>4 g/day) and estimated glomerular filtration rate (<35 ml/min) at diagnosis, establishing a staging system that identifies patients at higher risk for progression to ESRD and dialysis (23). A delay in diagnosis therefore dramatically impacts on patients' quality of life and survival. However, renal failure due to AA amyloidosis is still the presenting feature that prompts clinical suspicion and diagnostic work-up for a hereditary AID in several cases (24).

Although kidney damage usually dominates the natural history and clinical presentation, AA amyloidosis is a sys-

temic disease and therefore other signs and/or symptoms should also herald the diagnostic suspicion (Fig. 1). Gastrointestinal manifestations, including bowel abnormalities and gastric symptoms such as heartburn, nausea, and vomiting, hepatosplenomegaly and orthostatic hypotension related to autonomic dysfunction may variably associate with kidney damage over the disease course. Sometimes progressive thyroid enlargement is observed, with preserved hormonal secretion (25). Compared with AL and ATTR amyloidosis, cardiac involvement is quite unusual at disease onset although it may occur with time and negatively impact on survival in patients that require dialysis. Infertility due to progressive testicular infiltration has been reported in young men with untreated familial Mediterranean fever (FMF) (26). Symptomatic adrenal insufficiency due to massive gland infiltration has been observed in advanced stages and may complicate the management of patients undergoing renal transplantation (27). Diagnosis requires demonstration of amyloid deposits in a tissue biopsy coupled with typing by immunohistochemistry or by proteomics-based techniques (28). Although amyloid infiltration is expected in AIDs, non-amyloid nephropathies have been reported in a proportion of FMF patients in different series, as discussed later (29). This points to the necessity of a histological proof of amyloid deposition in all patients with an AID who develop renal dysfunction. Moreover, accurate definition of the amyloidogenic precursor has been thoroughly highlighted as a potential pitfall in the diagnosis of any systemic amyloid disease. AA amyloidosis is a long-term complication of AIDs as well as of many other chronic inflammatory conditions and mostly occurs in adult life, thus coexistence with a monoclonal gammopathy of uncertain significance is possible and requires the unequivocal characterisation of amyloid at the molecular level to rule out the most common AL amyloidosis. Non-invasive approaches, including an abdominal fat aspirate, a minor salivary gland or a gastroduodenal biopsy, should first be taken into

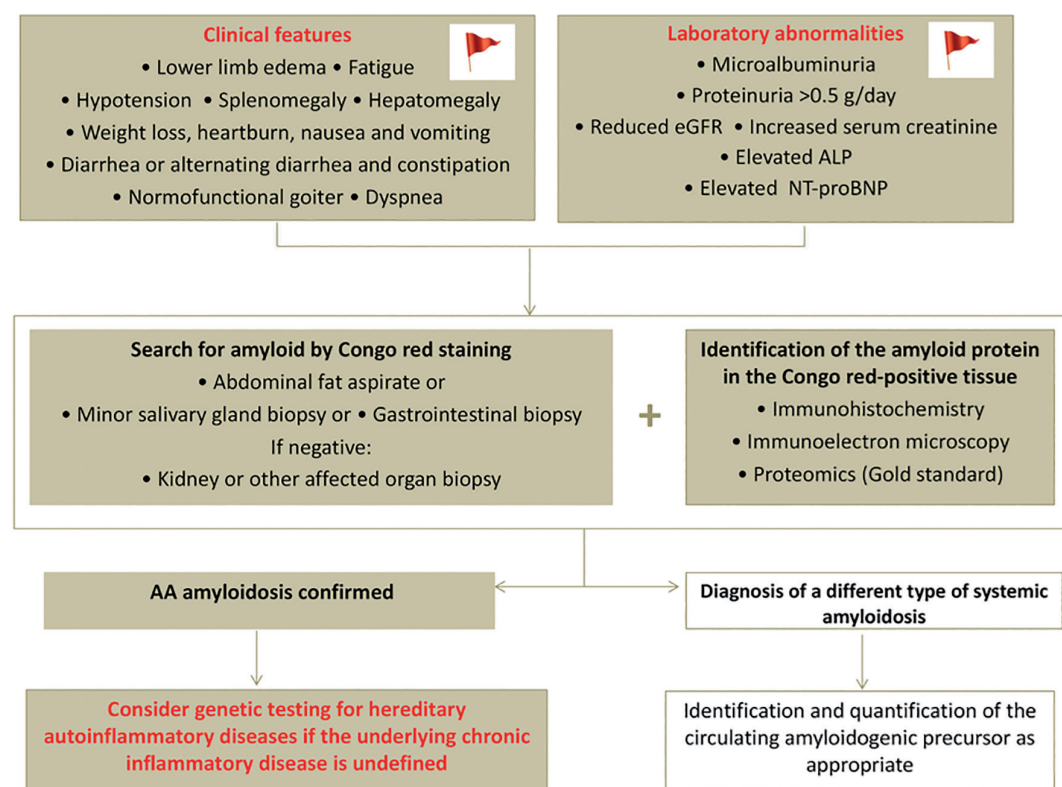


Fig. 1. Red flag signs and symptoms that should raise the suspicion of systemic amyloid A amyloidosis and recommended diagnostic work-up. AA: amyloid A; ALP: alkaline phosphatase; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro B-type natriuretic peptide.

consideration in order to minimise bleeding risks, although the feasibility of kidney biopsy is now widely supported in experienced centres (30). Prevention of AA amyloidosis is mandatory in patients diagnosed with a hereditary AID. Although no evidence-based guidelines are available to address optimal monitoring of AA risk, accurate surveillance can be performed by means of a periodic assessment of inflammatory markers and microalbuminuria during symptom-free intervals. Where available, evaluation of asymptomatic amyloid deposition in liver, spleen and kidneys using serum amyloid P component scintigraphy has been proposed. Beyond the intensity and duration of the systemic inflammatory process, additional factors that modulate the occurrence of AA amyloidosis have been identified (4). In particular, allelic heterogeneity at the *SAA1* locus, resulting in different genotypes, has been shown to play a role in promoting or reducing the risk of amyloid formation (31). Homozygosity for the *SAA1.1* allele is associated with a significantly higher risk of developing AA amyloidosis in Caucasians, whereas susceptibility is increased in individ-

uals carrying only the *SAA1.3* isoform in the Japanese population (32). The underlying mechanisms and the reasons for this discrepancy are far from being clarified, although it has been suggested that they might be related to a variable susceptibility of the different SAA isoforms to proteolytic cleavage (33). In clinical practice, assessment of the *SAA1* genotype may provide invaluable information for the management of patients with a poorly controlled hereditary AID, allowing the guidance of treatment choices and target SAA suppression according to risk. Whether other mechanisms have an impact on the risk of kidney damage and/or its progression in AIDs is not known. The inflammatory process that takes place in AIDs is not expected to directly injure the kidneys but, at least in FMF, there is evidence that 40-50% of patients presenting with proteinuria are not affected by renal amyloidosis and otherwise suffer from a primary glomerulopathy (29). Interestingly, a significant contribution is represented by IgA nephropathy (IgAN), the most common primary glomerulonephritis (34). Recently, the outcome of kidney donors who carry a *MEFV* gene muta-

tion was compared with that of control donors (35). This study showed that *MEFV* carriers had a significantly higher 24-hour proteinuria compared with the control group ($p=0.004$) four years after the donation raising the question whether this could be related to a sub-clinical inflammatory profile of these individuals. In this respect, increasing evidence linking innate immunity and NLRP3 inflammasome activation to the pathogenesis of several forms of acute and chronic kidney disease highlights the question as to whether additional local inflammatory mechanisms might also contribute to renal damage in patients with AIDs.

The role of the NLRP3 inflammasome in chronic kidney disease

Inflammation is known to play a role in the development of many acute and chronic non-infectious renal diseases, contributing to the extent of kidney damage and to the severity of organ dysfunction (36, 37). The inflammatory process is mediated by different pro-inflammatory cytokines that induce recruitment and infiltration of mononuclear inflammatory cells in renal tissue (38). The presence of these

cells in the damaged renal interstitium has been shown to correlate inversely with renal function (39, 40). Infiltration of inflammatory cells is responsible for tissue remodelling and kidney damage, including disruption of tubular integrity, accumulation of fibroblasts, tubular atrophy, and deposition of extracellular matrix molecules. These pathophysiological events are invariably associated with renal function deterioration (41), and consistently, interstitial inflammation and fibrosis are main predictors for the risk of progression towards ESRD (42).

In recent years, increasing research has been devoted to unveiling the molecular mechanisms involved in inflammation-mediated kidney damage. Circulating levels of both the proinflammatory cytokine IL-1 β and its naturally occurring receptor antagonist (IL-1Ra) are elevated in chronic kidney damage (CKD) and in dialysis patients, as also are IL-6 and IL-18 (8, 43, 44). Based on these findings, and on evidence that the NLRP3 inflammasome is involved in acute kidney injury in experimental renal ischaemia-reperfusion injury (45), investigations have progressively focused on the role of innate immunity, danger signalling, and inflammasome activation in the pathogenesis of CKD (46).

The role of the NLRP3 inflammasome in mediating renal inflammation in CKD was originally investigated in unilateral ureteral obstruction (UUO), the experimental mice model of chronic progressive renal injury. NLRP3 $-/-$ mice had less tubular injury, inflammation, and fibrosis after UUO, associated with a reduction in caspase-1 activation and maturation of IL-1 β and IL-18, compared with wild-type mice (47). In human CKD, up-regulation of the NLRP3 inflammasome was observed in kidney biopsies from a wide variety of non-diabetic kidney diseases, addressing the functional role of the caspase-1-IL-1 β -IL-18 cascade in mediating inflammatory damage (47). Inflammasome components are expressed in renal dendritic cells and macrophages and mediate NLRP3 canonical function, resulting in increased IL-1 β secretion. Expression has also been observed in

renal non-immune cells, including tubular epithelial cells. Renal interstitial inflammation has also been reported in kidney biopsies from patients affected by diabetic nephropathy (48) and localises in renal tubular cells.

Overall, there is increasing evidence, mostly gathered through experimental disease models, that the NLRP3 inflammasome plays a major role in mediating the inflammatory response underlying chronic tubulointerstitial diseases, including UUO, glomerulonephritis, and calcium oxalate crystal nephropathy (46).

Although it was initially reported that glomerular parenchymal cells fail to produce IL-1 β during sterile inflammation and the NLRP3 axis does not contribute to glomerular inflammation (49), activation of the inflammasome has more recently been suggested to play a role in different glomerular disease murine models. Experimentally, hyperhomocysteinemia (hHcys)-induced glomerular injury was demonstrated via formation and activation of the NALP3 inflammasome complex in podocytes, resulting in podocyte injury and glomerular inflammation, leading to glomerulosclerosis, independently of hypertension (50). Several studies indicate a crucial role of hHcys in the development and progression of renal damage associated with local inflammation, oxidative stress, impaired cell metabolism and consequent fibrogenesis; indeed, NLRP3 was reported to be activated in podocytes during hHcys (50). Treatment of podocytes with L-homocysteine induced the formation of NALP3 inflammasome complex, an increase in caspase 1 activity, rearrangement of the podocyte cytoskeleton, and decreased production of vascular endothelial growth factor (51). Reactive oxygen species (ROS) production observed in hHcys has been suggested to play a role in NLRP3 activation in podocytes and ultimately, glomerular injury. Furthermore, considering that glomerular VEGF is primarily produced in podocytes and hHcys-treated podocytes display significantly impaired secretion of VEGF, it was recently shown that hHcys treatment significantly increased cleavage of pro-caspase-1 into active

caspase-1, an important parameter of inflammasome activation (52). This study also reported that docosahexaenoic acid, a well-known ω -3 polyunsaturated fatty acid, suppressed inflammation via abrogating hHcys-induced podocyte injury by inhibition of the NLRP3 inflammasome activation. However, whether these cells undergo NLRP3 upregulation and have a functional role in canonical inflammasome activation in humans remains elusive and a non-canonical NLRP3 role in mediating fibrosis has been suggested (53).

Recently, several studies suggest that the NLRP3 inflammasome may also be implicated in the pathogenesis of the most common primary glomerulonephritis, IgAN, characterised by various degrees of intrinsic cell proliferation, especially of mesangial cells. Compared with control kidneys, NLRP3 gene expression was reported to be increased in renal biopsies of patients with IgAN and to correlate with disease clinical outcomes (54). This study also showed that although NLRP3 expression in IgAN was detected in glomeruli, it remained mostly confined to the tubular epithelial compartment.

Overall, the causal relationship between the inflammasome and the pathogenesis of IgAN is yet to be determined. A recent study has suggested the NLRP3 inflammasome plays a pathogenic role in the development of IgAN in part by activation of T cells, and mitochondrial damage and ROS production (55). Renal protein levels of NLRP3, IL-1 β , and IL-18 were significantly increased in the IgAN model in wild type mice and, moreover, improved proteinuria and renal function and milder renal lesions in IgAN in NLRP3 knockout mice was reported.

Proteinuria activates NLRP3 inflammasome upregulation

Proteinuria has been reported as an independent prognostic factor for long-term renal disease progression, and reduction of urinary protein excretion limits renal function decline in patients with non-diabetic and diabetic nephropathies associated with remodelling of the glomerular architecture

(56). Increased proinflammatory cytokine secretion mediates progressive proximal tubular damage and interstitial fibrosis associated with exposure to proteinuria. In a mouse model, albumin overload activates NLRP3 inflammasome by ROS (52). Fang *et al.* have elegantly shown that NLRP3 activation in kidney biopsy specimens was associated with the degree of albuminuria and that *in vitro* inflammasome upregulation depends on endoplasmic reticulum stress induced by albumin (57). Albumin reabsorption mediated by megalin/cubilin endocytic receptors on tubular epithelial cells leads to lysosomal dysfunction and cathepsin B release, which induces NLRP3 activation. Consequently, inhibition of cathepsin B or megalin/cubilin reduces albuminuria-induced tubular damage (57). Proteinuria may also act on podocytes. Furthermore, podocyte loss via apoptosis may be important in the development of glomerulosclerosis, as described in the model reported by Li *et al.* (52), in which the link between NALP3 inflammasome and podocyte damage was described experimentally in hHcys-induced glomerular injury.

Management of inflammation-mediated kidney damage:

AA amyloidosis and beyond

AA amyloidosis is still a challenging complication of hereditary AIDs, with prognosis depending on both early diagnosis and prompt management of the underlying inflammatory process. Rapid and effective suppression of SAA is associated with a favourable outcome, provided kidney failure is not too advanced (23). Management should aim at normalising SAA and C-reactive protein concentrations (22) within the shortest period of time. Thus, a close assessment of both inflammatory markers is mandatory to carefully monitor treatment response and guide the management strategy. The need for a rapid and effective suppression of the amyloidogenic precursor, combined with the increasing availability of specific drugs that inhibit either IL-1 β or IL-6, the two proinflammatory cytokines that regulate SAA hepatic transcription, has progressively changed the management

approach to AA amyloidosis. Although colchicine is still recommended in patients with FMF-related AA amyloidosis, the key role of IL-1 β in the pathogenic cascade of this disease should prompt us to consider IL-1 β inhibition as the first-line option in these patients, particularly when reduced renal function and/or possible gastrointestinal amyloid-related abnormalities may limit colchicine safety, with suboptimal treatment response at the maximum tolerated doses. However, association with colchicine during treatment with a biological agent is still recommended in FMF, whenever possible, based on the long-term evidence of its beneficial effect on AA amyloidosis in this context (58). Several reports have documented the rapid and dramatic response to IL-1 inhibition in patients with renal amyloidosis due to FMF, with a reduction in proteinuria and stability in kidney dysfunction, combined with a good safety profile (59-61).

Extensive experience has been consistently gathered in cryopyrin-associated periodic syndrome (CAPS) and tumour necrosis factor receptor-associated periodic syndrome (TRAPS) patients affected by renal AA amyloidosis with severe nephrotic range proteinuria and renal insufficiency (62, 63). More recently, the same approach has been used in patients with *MVK* deficiency developing renal amyloid complications. Unfortunately, response to IL-1 inhibition is less satisfactory in this patient population, whom possibly have more complex molecular mechanisms involved (64, 65). As IL-6 is the major driver of SAA secretion, IL-6 inhibition appears to be a successful tool in all patients with renal AA amyloid disease refractory to previous treatments (66). However, the long-term safety profile of this approach and its feasibility in patients that are known to be at higher risk for infectious complications, remains to be established.

Targeting the inflammasome in chronic kidney diseases

Although much of our knowledge regarding the role of the inflammasome in kidney injury is limited to experimental models and its contribution to

human renal disease has yet to be fully elucidated, the inflammasome is an attractive potential therapeutic target not only in renal AA amyloidosis but also in a variety of non-amyloid chronic renal disorders (36, 37). Moreover, IL-1 inhibition may be addressed to target the chronic systemic inflammatory process that is associated with CKD. Circulating levels of both the proinflammatory cytokine IL-1 β and its naturally occurring receptor antagonist (IL-1Ra) have been reported to be elevated in patients with CKD, regardless of the aetiology (8, 43, 44). Cardiovascular (CV) risk is substantially increased in patients with CKD who exhibit chronic systemic inflammation. Because chronic inflammation contributes to vascular dysfunction, it has been proposed that blocking inflammation may reduce CV risk in patients with CKD (67).

Conclusions

A long-lasting, systemic inflammatory process, as observed in inadequately treated or late-recognised hereditary AIDs, may lead to the development of AA amyloid-related organ damage, particularly at the kidney level. This complication has a dramatic impact on the natural course of AIDs, significantly worsening a patients' prognosis and quality of life. Promoting awareness is of the utmost importance in light of the availability of effective management approaches that specifically switch-off the underlying IL-1 β -mediated inflammatory process, potentially reverting organ damage and improving the outcome when established in the very early disease stage.

Acknowledgments

The authors acknowledge Dr Melanie Gatt for Health Publishing & Services Srl, for her English language assistance.

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