Treatment of De Novo and Recurrent Membranous Nephropathy in Renal Transplant Patients

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Membranous nephropathy (MN) is one of the common glomerular diseases diagnosed in transplanted kidneys. The exact impact of posttransplantation MN on the risk for graft loss and long-term graft outcome is not defined clearly. In recent reports, it has emerged as the third most frequent glomerulonephritis (de novo or recurrent) associated with renal allograft loss. Most cases of posttransplantation MN are thought to be idiopathic but cases associated with established secondary causes also have been reported. Patients can present with varying degrees of proteinuria and graft dysfunction. Risk factors that predict a poor outcome are not well established and unlike MN in the native kidneys, spontaneous remission is rare. Patients should be evaluated carefully for complications associated with nephrotic syndrome or graft dysfunction and managed accordingly. The beneficial effects of steroids, cyclosporine, mycophenolate mofetil, cyclophosphamide, chlorambucil, or other agents have not been validated. The role of specific treatments in cases of secondary MN is uncertain. Retransplantation is a reasonable option for patients who develop graft failure secondary to MN.

WITH ADVANCES IN immunosuppression, graft loss caused by acute rejection has decreased significantly over the past 2 decades. As long-term graft survival continues to improve, recurrent glomerulonephritis has emerged as the third most frequent cause of allograft loss, behind chronic rejection and death with a functioning graft.[1,2]

Several investigators have tried to estimate the prevalence and impact of de novo and recurrent glomerular diseases, including membranous nephropathy (MN), in transplant recipients.[2-4] However, most of the information published on this important problem is limited to retrospective reviews and case reports, based on the experience of individual transplant centers over many years.[5-8] As a result, with a limited number of cases at each center, differences in practice patterns, and duration of follow-up the reported frequency and effect of MN on allograft survival is extremely variable. Over the past few years, data from transplant registries has been available and likely will enhance our understanding of de novo and recurrent glomerular diseases in renal allografts. In 2 recent reports based on these data, posttransplantation MN emerged as the third most frequent type of glomerulonephritis resulting in graft loss.[2,3]

The diagnosis of MN in the renal allograft is based on histologic and electron microscopic features characteristic of this disease.[9] MN after transplantation can present as either recurrent or de novo disease. MN in renal allograft recipients is called de novo MN if it was never present in the native kidneys. On the other hand, MN is called recurrent if it occurred in the native kidneys before the transplant.

There has been some controversy as to whether de novo and recurrent MN are separate entities. At least one report suggests that most or all "recurrent" MN could be de novo disease occurring coincidentally in patients in whom MN was the original disease.[10] Conversely, it is possible that in cases in which a histologic diagnosis of native kidney disease was not available, recurrent disease may have been described mistakenly as "de novo" MN. In view of the reports of recurrence of recurrent MN in successive kidney transplants, recurrent MN is now accepted as a distinct entity.[11,12]

Both de novo and recurrent diseases may be classified further as idiopathic MN, in which no specific cause of MN could be detected, or secondary MN in the setting of an identifiable cause of MN.[13] Secondary MN in transplanted kidneys, especially in association with malignant tumors, is not well described.

EXTENT OF THE PROBLEM

Prevalence of De Novo and Recurrent MN

Although it is difficult to establish the exact prevalence of MN in the renal allograft, several

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studies have attempted to identify the extent of the problem. In a retrospective analysis, Hariharan et al[3] reported a total of 16 cases of MN among 4,913 patients studied at 6 different transplant centers in the United States from October 1987 to December 1996. Eight of the 16 patients were found to have de novo MN, and 8 were diagnosed with recurrent disease.

Truong et al[5] reported a series of 9 transplant patients with de novo MN among the 413 patients transplanted at their center, with a prevalence rate of 2.2%. Furthermore, at the time of publication of these data in 1989, the investigators were able to identify only 95 previously reported cases of de novo MN in transplant patients.

Schwarz et al[6] described the outcome of 700 renal transplants in 611 patients. Recurrence of MN was observed in only 1 of the 10 patients, whereas de novo MN presenting with varying degrees of proteinuria was diagnosed in 14 patients. Eleven of these 14 patients with de novo MN also had histologic features suggestive of chronic allograft nephropathy, and in at least 2 cases MN was linked to hepatitis B virus infection. Graft loss was reported in only one patient with de novo disease.

In a subsequent report, Schwarz et al[7] evaluated 1,029 renal transplants in 848 patients between 1970 and 1992, and reported de novo MN in 21 patients. The investigators found that de novo MN was the second most common cause of nephrotic range proteinuria in transplant recipients behind chronic allograft nephropathy.

The prevalence rates of de novo MN in kidney transplant recipients quoted in other studies vary between 0.4% to 9.2%.[8,14-17] This discrepancy in prevalence rates at different transplant centers is likely owing to variations in clinical practices of how frequently proteinuria is checked or biopsy procedures performed, or possibly the consequence of differences in duration of follow-up.

Recurrent MN has long been considered a rare entity, with medical literature limited to sporadic case reports. However, studies of recurrent MN over longer periods of time have found recurrence rates as high as 29% to 50%.[3,8,18]

Briganti et al[2] recently reported graft loss owing to recurrent disease in 5 of the 81 patients with a history of MN transplanted between 1988 and 1997. In this study, recurrence was only detected when it caused allograft loss.

With improved long-term graft survival, and older patients now being considered for transplantation, the incidence of MN is expected to increase.[14] Moreover, it is likely that the actual incidence of disease is underestimated because the diagnosis can be missed in patients who present with subclinical disease.

In most cases of de novo or recurrent MN in the renal allograft, a secondary cause is not identified. Among the 22 cases of posttransplantation MN reported by Monga et al,[8] only one patient tested positive for hepatitis C and a second patient was found to have pancreatic cancer 30 months after transplantation. Similarly, Steinmuller et al[19] described 2 cases of de novo MN, one associated with hepatitis B and the other with renal infarction.

Morales et al[20] have reported 15 patients with chronic hepatitis C who developed allograft MN. Ten of these cases were thought to be de novo MN. Schwarz et al[7] found hepatitis B, C, or human immunodeficiency virus antibody in 8 of the 21 patients with de novo membranous nephropathy. The role of other causes of secondary MN is not well defined and there are limited reports of posttransplantation MN in patients with a history of systemic lupus erythematosus, ureteral obstruction, and antiglomerular basement membrane disease.

CLINICAL FEATURES

De Novo MN

De novo disease has been described in transplant recipients of all ages. It generally manifests with a variable degree of proteinuria, with or without a decline in graft function, and has been diagnosed at any time during the posttransplant period.

In a series described by Truong et al,[5] de novo MN was diagnosed in 10 transplant recipients ranging in age from 15 to 54 years. Eight of the patients were men. Six patients had nephrotic range proteinuria. The serum creatinine concentrations in patients with nephrotic range proteinuria ranged from 1.1 to 2.8 mg/dL, and 4 patients had a serum creatinine concentration of 2 mg/dL or greater. Graft failure occurred in 5 of the 6 patients with nephrotic range proteinuria 9 to 31 months after transplantation. In contrast, none of the 3 patients with documented subnephrotic proteinuria developed graft failure after greater than 90 months of follow-up. The time from diagnosis of MN to graft failure ranged from 2 to 42 months.

From this study it appears that patients with nephrotic range proteinuria or evidence of graft dysfunction at the time of diagnosis tend to have poor prognosis.

Cosyns et al[21] described 9 patients with de novo MN who presented with nephrotic range proteinuria between 11 and 30 months posttransplantation. The outcome in this series was poor with 5 of 9 patients developing graft failure within 4 to 26 months of diagnosis.

Monga et al[8] identified 22 patients with MN in the allograft. Fifteen patients had de novo MN, diagnosed between 9 and 81 months after transplantation. Eleven patients had nephrotic range proteinuria, and serum creatinine values at the time of diagnosis ranged from 0.9 to 10 mg/dL. Seven patients developed graft failure within 9 to 48 months of transplantation, 2 had gradually declining graft function, and the remaining 5 maintained normal function for the duration of the study period.

The earlier studies suggest that de novo MN can present at any time after transplantation and in most cases is heralded by either a decline in graft function or new-onset proteinuria. Graft outcome in de novo disease is variable, with some patients progressing to graft failure, and others maintaining stable graft function. Spontaneous remissions, partial or complete, are uncommon, but have been reported in de novo as well as recurrent disease.[5,22]

Recurrent MN

Recurrent MN has been described in both cadaveric and living kidney transplants, and similar to de novo disease, presents with proteinuria, with or without graft dysfunction. Recurrent MN also can present at any time after transplantation. Lieberthal et al[23] described a patient with recurrent MN who had recurrence with nephrotic range proteinuria a week after transplantation. However, despite this early recurrence and persistent nephrotic range proteinuria, the patient's graft function remained stable a year after transplantation.

Cosyns et al[18] described the outcomes of 12 patients who were transplanted for renal failure secondary to MN. Ten of the 12 patients were men. MN was considered idiopathic in 11, and was associated with chronic hepatitis B virus infection in one patient. During follow-up, recurrent MN was diagnosed in 3 patients. All developed nephrotic range proteinuria at 2, 4, and 5 months and lost their grafts at approximately 2, 4, and 10 years posttransplantation. Mean duration of MN in native kidneys, duration of pretransplant hemodialysis, human leukocyte antigen DR3, living donation, and use of cyclosporine did not affect outcome.

Monga et al[8] described 3 cases of recurrent MN presenting at 28, 30, and 63 months after transplantation; and all 3 patients eventually developed graft failure.

Briganti et al,[2] however, reported only 5 cases of graft failure over a 10-year period among the 81 patients with recurrent MN.

Recurrence of Recurrent MN

Recurrence of MN in successive kidney transplants, although rare, also has been reported. In 2 separate case reports the patients had fairly aggressive native kidney disease characterized by complications and eventual graft failure. In the first case, recurrent MN presented with nephrotic range proteinuria at 12 months after the first transplant, and progressed to graft failure within 6 months, warranting retransplantation. Unfortunately, the disease recurred again, and was diagnosed at 12 months after the second transplant. Despite recurrence, the graft continued to function for greater than 4 years after the diagnosis.[11]

In another case described by Innes et al,[12] recurrence was diagnosed at 26 months after the first transplant, leading to graft failure 16 months after diagnosis. After retransplantation, MN recurred within 5 months with progressive decline in renal function. Apart from diuretics and angiotensin-converting enzyme inhibitors, no specific therapy for MN was administered in either of these 2 cases.

Lazowski et al[24] described recurrent crescentic MN in 2 successive renal transplants, leading to graft failure. Interestingly, recurrence was associated with choroidal effusions and retinal detachments but an exhaustive work-up to exclude a secondary cause for MN was unremarkable. Treatment with high-dose steroids and cyclophosphamide was ineffective.

These reports suggest that there is marked variability in the presentation of recurrent MN, even when presenting in successive transplants in the same patient. Furthermore, at least one report suggests a possible role for retransplantation in patients with graft loss owing to recurrent MN.[11]

ISSUES AND CHALLENGES

Membranous nephropathy, although a common cause of nephrotic syndrome in adults, has a highly variable course, ranging from a progressive decline in renal function to spontaneous remission, even in the absence of medical intervention.[25] Although treatment protocols exist for native kidney disease, treatment guidelines for recurrent or de novo membranous nephropathy are sketchy, and anecdotal at best. The difficulties encountered in defining treatment strategies for patients with de novo or recurrent MN in transplant recipients are enhanced further by factors discussed later.

Impact of De Novo or Recurrent MN on Graft Outcome

The overall impact of MN, both recurrent and de novo, on graft function remains unclear. Briganti et al[2] reported a 10-year incidence of 8.4% of allograft loss owing to recurrent glomerular diseases. Despite the effect of recurrence, the 10-year incidence of allograft loss was similar among transplant recipients diagnosed with glomerulonephritis affecting the allograft and those with other causes of renal failure. In this report, although the 10-year cause-specific incidence of graft loss in patients with MN was 40.1%, graft failure attributable primarily to recurrent MN was only 12.5%. Furthermore, recurrent MN in this study was not associated with an increased risk for graft failure.

Similarly, on analyzing the Renal Allograft Disease Registry data, Hariharan et al[3] could not find any increased risk for graft failure in patients with de novo or recurrent posttransplantation MN. Berger et al[15] also have described 6 patients in whom de novo MN did not adversely affect graft survival. In contrast to these observations, Cosyns et al[21] described 9 patients with de novo MN of whom 5 developed graft failure within 4 to 26 months after the onset of nephrotic syndrome.

A few recent studies could not identify any distinct adverse effect on the rate of graft failure but a trend toward an increase in the rates of allograft loss caused by MN, over time, was observed.[2,18] Based on these observations, no definite conclusion can be drawn on the impact of de novo or recurrent MN on graft outcomes.

Risk Factors for De Novo or Recurrent MN

Efforts to identify factors that would predict the risk for developing de novo or recurrent disease have not been successful to date. However, although there are no specific individual risk factors that predict poor outcome, heavy proteinuria in hypertensive male patients may be associated with a poor outcome.[5,8] Hariharan et al[2] observed a male preponderance in cases of de novo or recurrent MN, with 94% of MN being diagnosed in men, but this difference was not statistically significant. Previous reports linking a good human leukocyte antigen match and transplantation of living related kidneys to higher rates of MN in transplant recipients have not been confirmed.[15,26]

Role of Immunosuppressive Therapy

Transplant recipients are on immunosuppressive regimens that traditionally include steroids, calcineurin inhibitors such as cyclosporine and tacrolimus, and antiproliferative agents such as azathioprine or mycophenolate mofetil. Although prednisone, and more recently cyclosporine and mycophenolate mofetil, has been used in the treatment of primary MN, there appears to be no protective effect of these immunosuppressive agents in the treatment or prevention of de novo or recurrent disease in kidney transplant recipients.[6,15,18]

Montagnino et al[27] compared the incidence of recurrent and de novo MN in 584 renal transplant patients treated with azathioprine-based immunosuppressive regimens, with or without concomitant cyclosporine. Of 263 patients treated with azathioprine alone, 3 patients were diagnosed with de novo MN. None of the 3 patients in this group who had MN as their original disease developed recurrent disease. In contrast, of the 321 patients who received cyclosporine, there were 5 cases of de novo MN. In addition 3 of the 6 patients with MN in their native kidneys developed recurrence. This study suggests that despite cyclosporine's possible benefit in treating native kidney MN, it does not confer any protective effect against recurrent or de novo MN.

Secondary MN in Renal Allografts

The association of recurrent MN with hepatitis B and C infections makes treatment difficult because there is concern that aggressive treatment of MN could result in progression of viral hepatitis.[20] Furthermore, limited evidence of the efficacy of treating other established causes of MN such as lupus, drug therapy, and occult malignancies

makes it difficult to establish treatment strategies for secondary MN in renal allografts.

TREATMENT OF MN IN KIDNEY TRANSPLANT RECIPIENTS

Treatment recommendations described later are based on the limited anecdotal evidence in transplant literature and extrapolation of data from our experience with MN in the native kidneys.

General Measures

The aim of such measures is to preserve renal function and manage the complications associated with nephrotic syndrome. The use of treatment strategies focusing on reduction of proteinuria and optimization of blood pressure control have never been evaluated extensively in patients with recurrent and de novo glomerular diseases of the renal allograft. However, based on the observations in native kidney diseases, use of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, which in addition to blood pressure control could confer antiproteinuric and renoprotective effects, may be considered as a first-line option.[28,29]

Treatment of hyperlipidemia, which is a serious complication of nephrotic syndrome, may be beneficial in transplant patients in whom cardiovascular disease is the leading cause of mortality.[1] Although the role of such therapy in the management of patients with posttransplantation nephrotic syndrome has not been defined clearly, Ideura et al[30] evaluated the role of low-density lipoprotein (LDL) apheresis in a patient with nephrotic syndrome owing to MN diagnosed 15 months after transplantation. The patient was hyperlipidemic with a total cholesterol level of 387 mg/dL. After failing a trial of intravenous pulse steroids, 12 LDL apheresis treatments were performed (2 treatments/wk for 6 weeks). Six months after treatment, the patient appeared to be in remission with a stable serum creatinine level, 24-hour urine protein level less than 0.5 g, and a total cholesterol level of 212 mg/dL. Because LDL peroxidation has been implicated as one of the causes of MN, the investigators hypothesized that LDL apheresis decreased the source of lipid peroxidation by lowering LDL levels, and thereby induced a MN remission. This novel role of LDL apheresis as effective therapy for allograft MN requires further validation.

Renal vein thrombosis complicating allograft MN also has been reported.[5,7]

Because renal vein thrombosis can result in allograft dysfunction, monitoring for such complications should be considered in suspected cases. Biesenbach et al[31] evaluated the risk for thromboembolic events in patients with recurrent glomerulonephritis after kidney transplantation. These investigators found an association with the degree of proteinuria, higher fibrinogen concentrations, and lower antithrombin III levels and thrombovenous and thromboembolic complications. They suggested anticoagulation therapy in the setting of severe proteinuria.

Patients with nephrotic syndrome could also be at an increased risk for infections. This risk is further enhanced in transplant recipients who are treated with immunosuppressive agents. Although no specific guidelines are available on monitoring or treatment strategies, including the use of prophylactic antimicrobial agents, early diagnosis of infection and initiation of appropriate therapy could be life saving.

Specific Measures

Role of Steroid Therapy

Oral as well as intravenous high-dose steroid therapy has been tried with varying results. Although some investigators have reported success with the use of intravenous pulse methyl prednisolone,[32] there does not appear to be any consistent response to this treatment.[5,6]

Truong et al[5] treated 3 patients with proteinuria owing to de novo MN with alternate-day, high-dose prednisone therapy. One patient had a partial remission, with proteinuria decreasing from 2.5 g/d to 543 mg/d after 2 months of treatment, whereas the 2 other patients given the same treatment did not respond. The investigators did not describe the dose of prednisone and also did not comment on other measures that might have contributed to the observed decline in the degree of proteinuria.

Schwarz et al[6] reported their experience with using steroid pulses in one patient with recurrent MN diagnosed 2 months after transplant. The therapy was ineffective in achieving remission. The patient lost the graft within 3 months of diagnosis.

Ideura et al[30] reported a 46-year-old man with native kidney disease of unknown cause who developed nephrotic syndrome owing to MN within a

year after receiving a cadaveric kidney transplant. Intravenous methylprednisolone, 1 g/d for 3 days, did not diminish the proteinuria. Similarly, Berger et al[15] have reported a lack of benefit with additional prednisone therapy in the setting of standard transplant immunosuppression.

Johnston et al[32] in 1993 described a 45-year-old woman who developed nephrotic syndrome 19 months after receiving a cadaveric renal transplant. She received 3 doses of 1 g intravenous methylprednisolone followed by 125 mg prednisolone on alternate days. The patient responded to steroid therapy, and at the last reported follow-up evaluation her kidney function was stable with minimal proteinuria.

In view of these contradictory reports, it is difficult to ascertain the role of high-dose steroid therapy in treating patients with allograft MN. Nevertheless, in view of the relative safety of short-term pulse steroid therapy, want of a specific therapeutic agent, and the suggested benefit observed in some patients, a controlled trial of steroid therapy may be considered in a subset of patients with a more aggressive disease course. Prolonged steroid use in these immunosuppressed patients would require close monitoring for steroid-induced complications.

Role of Immunosuppressive and Cytotoxic Drugs

As discussed earlier, the use of steroids and cyclosporine do not appear to confer any protective or therapeutic benefit in preventing de novo and recurrent MN or in altering graft and patient outcomes.[5,15] Cosyns et al[18] described 2 patients with recurrent MN on azathioprine-based immunosuppression who were switched from azathioprine to cyclophosphamide and cyclosporine. In both of these cases, the proteinuria persisted despite the change in immunosuppression. In the patient switched to cyclophosphamide, the disease course was characterized by a rapid decline in graft function, with progression to graft failure within 2 years of diagnosis. On the other hand, in the patient converted to cyclosporine, the disease followed an indolent, gradually progressive course, ultimately resulting in graft loss at 10 years. This difference in outcome may represent the natural history of the disease rather than a beneficial effect of cyclosporine because the patient had persistent nephrotic range proteinuria despite initiating this therapy. A review of the potential risk factors for recurrence of MN suggested no benefit with the use of cyclosporine because 4 of the 8 patients who had recurrence were on cyclosporine as compared with 12 of the 22 patients who did not experience recurrence.

Schwarz et al[6] have reported the clinical course of 14 patients with de novo MN treated with or without cyclosporine. MN was observed in 2.4% of all functioning transplants and the incidence was not different in the patients treated without and those who were treated with cyclosporine.

To our knowledge, there are no reports to suggest a definite therapeutic advantage with the use of tacrolimus as compared with cyclosporine in the treatment or prevention of MN in transplant recipients.

These observations do not suggest any benefit from the use of cyclosporine or other such agents and appear to challenge earlier views that the use of newer immunosuppressive drugs, many of which are used for treating primary GN, would decrease the incidence of recurrent and de novo glomerular diseases in the renal allografts, or at the very least mitigate the course of disease.

Role of Retransplantation

Based on anecdotal reports of retransplantation after allograft loss to recurrent disease, retransplantation appears to be a rational option.[11] There is no strong evidence to suggest that patients with MN in the previous graft would be at an added risk for subsequent graft loss. However, patients should be counseled about the risk for disease recurrence in the second transplant and possible progression to graft failure.

Treatment of Secondary MN

Once the diagnosis of posttransplantation MN is made, it may be useful to distinguish idiopathic from secondary MN. Screening for hepatitis B, hepatitis C, and lupus should be considered, although it is unclear whether identifying these causes of secondary MN will improve graft outcome. Although there are no reports validating screening for occult malignancy, the use of such measures as dictated by clinical suspicion may be beneficial in early diagnosis of a malignant condition and could impact patient survival.[33]

The role of pulse steroids in patients with hepatitis B– or C–induced MN has not been delineated clearly. Morales et al[20] described 15 patients with chronic hepatitis C virus infection who developed

MN with proteinuria. Of these, 5 patients were treated with 250 mg of methylprednisolone for 3 consecutive days, followed by 1 mg/kg/d of prednisone for perhaps 6 weeks, and eventually tapered to a maintenance dose of 10 mg/d. Two of the 5 patients had partial remissions of proteinuria within an average of 4 months. In the 10 untreated patients, proteinuria persisted, and 8 patients lost their grafts secondary to MN and chronic rejection. All 5 patients treated with steroids had functioning grafts at an average of 12 months after diagnosis. These findings are provocative because the patients who received steroid therapy appeared to have had a better outcome. The investigators did not offer any explanation for the observed differences in survival rates that seemed to show a benefit in the treated as compared with the untreated group.

Safety of antiviral agents, such as interferon alfa, to treat patients with MN secondary to hepatitis B or hepatitis C virus infection, given the paucity of literature in the posttransplantation setting, and the inherent risk for precipitating a rejection episode, has not been confirmed.

Because recurrence of lupus nephritis after kidney transplantation is uncommon, medical literature on lupus-associated MN in the allograft is limited. In a recent case report of lupus-associated MN in the allograft, Denton et al[34] observed that mycophenolate mofetil was associated with sustained reduction of proteinuria and stable graft function.

Although further studies are required to confirm the efficacy of mycophenolate mofetil in treating lupus-associated MN in the allograft, switching to an immunosuppression regimen that includes mycophenolate may be considered in such patients.

CONCLUSIONS

Posttransplantation MN remains an enigma, with a high degree of variability in the disease course and reported outcomes. Because treatment strategies are limited by lack of prospective studies, we are forced to seek answers from our experience with native kidney MN, retrospective studies in the transplant literature, and anecdotal reports.

Management of posttransplantation MN should be individualized, with emphasis placed on institution of general measures and modification of risk factors to minimize associated complications. These measures include, but are not limited to, optimizing blood pressure control, implementing strategies to reduce proteinuria, and management of hyperlipidemia.

The benefit of screening for secondary causes of MN such as hepatitis B and C virus infections, systemic lupus erythematosus, and malignancy in these patients should be evaluated carefully because identification of such underlying factors may have important implications for graft and patient survival.

The substitution or addition of other therapeutic agents including high-dose steroids, cyclosporine, and mycophenolate mofetil, which are used routinely as antirejection therapy, has not been proven beneficial in patients with posttransplantation MN.

Given the lack of data to suggest any benefit, and potential for serious side effects, use of cyclophosphamide and chlorambucil should be considered only with extreme precaution. Finally, retransplantation remains a suitable option for otherwise healthy patients who develop graft failure secondary to MN.

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