Amyloidosis diagnosed in solid-organ transplant recipients

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Abbreviations page

AA- AA amyloidosis (previously known as secondary amyloidosis)

AL- AL amyloidosis (previously known as primary amyloidosis)

CR- complete response

CRP- C-reactive protein

MGUS- monoclonal gammopathy of undetermined significance

NR- no response

PCN- plasma cell neoplasia

PD- progressive disease

PR- partial response

PTLD- post-transplant lymphoproliferative disorder

SAA- serum amyloid A protein

VGPR- very good partial response

wtATTR- wild type transthyretin amyloidosis

Abstract

Background

Development of amyloidosis post solid organ transplantation has not been reported, although plasma cell neoplasms are a rare form of post-transplant lymphoproliferative disorder which could be complicated by AL amyloidosis.

Methods

We searched our database of 5,112 patients seen between 1994-2018 with a diagnosis of amyloidosis post solid organ transplant. Patients were excluded if the amyloid diagnosis preceded the transplant date. The indication and type of organ transplant were recorded in addition to the amyloidosis type, organs involved, treatment given and survival.

Results

Thirty patients were identified. The median age at diagnosis with amyloidosis was 52 (range 33-77) years. The median time from transplantation to diagnosis was 10.5 (0.58-36) years. The grafts were: kidney (N=25, 83.3%), liver (N=2, 6.7%) heart (N=2, 6.7%) and combined heart, lung and kidney (N=1, 3.3%). The type of amyloidosis was: systemic AL (N=14, 47%), AA (N=11, 37%), localised AL (N=3, 10%), wild type transthyretin (wtATTR) (N=1, 3.3%) and amyloid of uncertain type (N=1, 3.3%). Renal graft dysfunction was seen in 11/25 (44%) cases. Median graft survival was 185 (96-269) months and median survival from diagnosis with amyloidosis was 45 (2-89) months; median survival by amyloidosis type was: localised AL, 64 (20-67) months, systemic AL, 23.5 (0-95) months, ATTR amyloidosis, 17 months, AA, 15 (0-77) months.

Conclusions

This series is the first description of amyloidosis post solid organ transplant; 30 cases among 5,112 amyloid patients over 24 years suggests that amyloidosis may occur post solid organ transplantation with an overall poor survival.

Introduction

Solid organ transplantation carries an increased risk of malignancy which has been attributed to the requirement for long term immunosuppression. Skin cancer is the most common malignancy, followed by post-transplant lymphoproliferative disorder (PTLD).[1] The risk of PTLD can be as high as 10% and is largely dependent on the type of organ transplanted with the highest risk in intestinal and the lowest in renal transplants, probably reflecting the degree of immunosuppression required;[2] age and length of time post-transplant are also recognised risk factors.[3]

The World Health Organisation provides a histological classification system for PTLD.[4] Approximately 85% of cases of PTLD are B cell in origin[5], and the plasma cell neoplasms (PCN) are a rare form of monomorphic type PTLD.[6] In a large study of 202,600 solid organ transplant recipients from the United States the estimated incidence of PCN was 15.4 per 100,000 person years, which represents a 1.8 fold increase compared with the general population.[7] The majority of cases described were multiple myeloma (N=102/140), with fewer cases of plasmacytomas (N=38/140).[7] No cases of systemic AL amyloidosis were described. Nonetheless systemic AL amyloidosis is a well-recognised complication of B cell disorders and is therefore a potential complication of PTLD. There is little in the literature regarding this risk presumably reflecting the rarity of both PTLD associated PCN and AL amyloidosis. Here we report a series of 30 UK patients diagnosed with amyloidosis following a solid organ transplant. Our hypothesis was that AL amyloidosis can develop after a solid organ transplant as a rare complication of PCN- PTLD.

Materials and methods

The National Amyloidosis Centre provides a tertiary referral service for patients with amyloidosis and related disorders in the UK. The target population is all English and Scottish patients with suspected and histologically demonstrated amyloidosis.[8] We searched our database of 5,112 patients with a diagnosis of amyloidosis seen from 1994-2018 for solid organ transplant. All patients had been referred to the National Amyloidosis Centre 427 cases were excluded as the diagnosis of amyloidosis preceded the transplant date. The indication for solid organ transplantation, the transplant date and the organ transplanted were recorded. In all cases amyloidosis was confirmed on biopsy material by Congo-red staining with demonstration of characteristic birefringence under cross polarized light. The amyloid fibril sub-type was established by immunohistochemistry using a panel specific antibodies or by mass spectrometry.[9,10] Where a definitive diagnosis was not made by immunohistochemistry, genetic testing was used to exclude hereditary amyloidosis. All patients had a detailed baseline assessment including organ function, imaging with SAP scintigraphy and echocardiogram and biomarker assessments.[11] Organ involvement with amyloidosis was defined according to the international amyloidosis consensus criteria.[12] Treatment details were recorded, including transplant immunosuppression and treatment aimed at the underlying amyloidogenic condition. Hematological responses were assessed at six months and organ response at 12 months, both calculated from the date of diagnosis and defined according to the international amyloidosis consensus criteria.[12] We also gathered details about the graft survival, where data were available.

Statistical analysis was performed using SPSS version 21. Survival outcomes were analyzed using the Kaplan-Meier method. Approval for analysis and publication was

obtained from the institutional review board at the University College London and written consent was obtained from all patients in accordance with the Declaration of Helsinki.

Results

Thirty patients (19 male, 11 female) were included.

i) Patient transplant characteristics

The 30 patients received solid organ transplants between 1970 and 2013. Details of the reason for organ transplantation, the organ type and the immunosuppressant taken at the time of diagnosis with amyloidosis are outlined in table 1. The median age at transplant was 44 years (range 10-71 years). The organ transplanted was kidney (N=25, 83.3%), liver (N=2, 6.7%), heart (N=2, 6.7%), with the final patient having a combined heart, lung and kidney transplant (N=1, 3.6%). The cause of organ failure was available in 67% of cases (20/30 patients) and are listed in table 1.

ii) Characteristics of amyloidosis

a. The entire cohort of patients

All 30 patients had histological confirmation of amyloid deposition. The median age at the time of diagnosis with amyloidosis was 52 years (range 33-77 years). The most frequent type of amyloidosis was light chain (AL) (N=14, 46.7%), followed by AA (N=11, 36.7%), localised AL (N=3, 10%), wild type transthyretin (wtATTR) (N=1, 3.3%) and amyloid of uncertain type (N=1, 3.3%). The median time from date of transplant to diagnosis of amyloidosis was 10.5 years (range 7 months to 36 years).

b. AL amyloidosis patient characteristics and treatment details

In the 14 patients with systemic AL amyloidosis, 12 were renal transplant recipients (N=12/14, 86%), one a liver transplant recipient (N=1/14, 7%) and the final patient had a combined heart, lung and kidney transplant (N=1/14, 7%), see table 2. The reasons for transplantation are outlined in tables 1 and 2. The median age at diagnosis with AL amyloidosis was 50 (33-77 years) and the median time from transplantation to diagnosis with amyloidosis was 12 years (7 months- 31 years). A monoclonal paraprotein was detectable in 50% (7/14 cases) at a median value of 4.5g/l (range 3-28g/l). The isotype was: IgG lambda in four cases, IgG kappa in two cases and IgA lambda in one case. The median concentrations of the amyloidogenic class of free light chain are outlined in table 2. Only one patient (N=1, 7%) was known to have had a monoclonal gammopathy of unknown significance prior to transplant. Details of the underlying clone were available in 13/14 patients and this was a plasma cell clone in all cases.

Organ involvement with AL amyloidosis was as follows: kidney (N=10/14, 71.4%), spleen (N=8/14, 57.1%), heart (N=5/14, 35.7%), liver (N=5/14, 35.7%) and soft tissues (N=1/14, 7.1%). Treatment details were available for 9/14 patients, eight patients received chemotherapy aimed at their amyloidogenic clone, table 2. The median number of lines of treatment was one (range 1-2 lines). The most common chemotherapy was a Bortezomib (N=6, 66.7%), followed by Thalidomide (N=2, 22.2%). Haematological response to treatment was assessed at 6 months; two patients (25%) achieved a complete response (CR) to treatment, one a very good partial response (VGPR) (12.5%), two a partial response (PR) (25%) two patients no response (NR) (25%) and one patient progressive disease (PD) (12.5%). Organ responses were assessed at 12 months for the same eight patients and are outlined

in table 2. Of the 15 patients with AL amyloidosis 11 (N=11, 79%) are either dead or have clinically relapsed with a median OS from diagnosis with amyloidosis of 23.5 months (0-95 months). In the eight patients who were treated, five patients (N=5, 63%) have progressed or died with a median progression free survival of 42 months (range 1-83 months).

c. AA amyloidosis patients

Of the 11 patients with AA amyloidosis two patients were recipients of a cardiac transplant (N=2/11, 18%) and the other 9 patients (N=9/11, 82%) were renal transplant recipients, see table 3. The median age at diagnosis was 57 years (40-73 years), and the time from transplant to the development of AA was 11 years (8 months-36 years). None of the patients had cardiac involvement, and the majority renal (N=7/11 63.6%) and splenic (N=6/11, 54.5%) involvement. The median presenting serum amyloid P (SAA) and C-reactive protein (CRP) are outlined in table 3. The median time from diagnosis to death or last follow-up was 15 months (0-77 months). An underlying chronic inflammatory disorder was overt in 5/11 (45%) patients, see table 3; an underlying cause was not clearly identified in 3/8 cases (38%), and was indeterminable (due to lack of clinical detail) in 3 cases (27%).

d. wtATTR patients

The patient in this series with wtATTR amyloidosis was male and 67 years old at the time of diagnosis with a renal transplant four years earlier for diabetic nephropathy. His presentation was with breathlessness with an NT-proBNP of 12770ng/L and a cTnT of 172ng/L. The time from diagnosis with wtATTR to death in this patient was 17 months.

e. Localised AL patients

Three patients had localised AL amyloidosis. The first patient was 57 years when diagnosed with localised laryngeal disease after a renal transplant 11 years previously for polycystic kidney disease. The time from diagnosis to death was 64 months (5.3 years). The cause of death was unknown, but there was no evidence of systemic amyloid disease. The second patient was 36 years at diagnosis with localised lymph node amyloidosis following a liver transplant 5 years previously following a paracetamol overdose. The time from diagnosis to death was 20 months. The final patient was 43 years at the time of diagnosis with localised gastrointestinal amyloidosis following a renal transplant 10 years previously for end stage renal failure of an unknown cause. The patient's median graft survival was 189 months and the cause for graft failure was unknown, but amyloidosis was excluded. The patient declined further follow up at 67 months from diagnosis.

iii) Patient survival and renal transplant outcomes

The median follow up was 21.5 months (range 0-95 months), defined from a diagnosis of amyloidosis to last follow up or death. In this time there were 19 deaths (63.3%). Detailed cause of death was not recorded. The median OS of all 30 patients, defined from date of diagnosis with amyloidosis to death or last follow-up was 45 months (range 2-88 months) and for each subtype of amyloidosis: localised AL, 64 months (20-67 months); systemic AL, 23.5 months (0-95 months); ATTR amyloidosis, 17 months; AA, 15 months (0-77 months).

Of the 25 patients with a kidney transplant, 11 patients had graft failure (44%). Median graft survival for all patients was 185 months (96-269 months) and in those patients whose grafts failed median graft survival was 2 months (range 2-64

months). The reasons for graft failure were available in 9/11 patients and are outlined in table 1.

Discussion

This series describes the characteristics of thirty patients who developed amyloidosis *de novo* following a solid organ transplant with a poor overall survival. Although there is clear grounds for concern about development of systemic AL amyloidosis post-transplant, as a complication of PTLD related production of monoclonal immunoglobulins, unexpectedly 11 patients (37%) had AA amyloidosis, implying substantial chronic inflammation following transplantation and highlighting the importance of comprehensive investigation to establish the amyloid type.

One patient developed wtATTR (otherwise known as senile cardiac amyloidosis). In 2008, the estimated age adjusted incidence of wtATTR, based on new referrals to the NAC, was 0·3/100 000 population;[8] but this is likely an under-estimation reflecting substantial under-diagnosis.[13] Given the increasing number of patients recognised over the last decade, it is likely that a proportion of older patients with solid organ transplants will develop unrelated wtATTR as they age. Our patient with wtATTR had a presentation and disease course in keeping with wtATTR patients without a concurrent transplant, other than his slightly younger age at diagnosis (63 years, compared with the median age at presentation of 73 years)[14] and a worse survival than predicted by disease stage (17 months, compared with an expected 32.7 months (95% CI 23.4–37.0 months)).

Three patients (10%) were found to have localised AL amyloidosis post transplantation in the larynx, lymph nodes and gastrointestinal tract respectively. Localised disease usually has a good prognosis and does not require systemic chemotherapy again demonstrating the importance of a full amyloid work up prior to considering cytotoxic treatments. Localised amyloidosis is well recognised and

assumed to be due to a focal clone of plasma cells within the local environment. In a large case series 12% of 5050 new amyloid referrals were localised AL disease.[10] The median OS of these three patients was shorter than expected with a median OS of 2.8 years compared to a 10-year overall survival for all forms of localised amyloidosis 80.3% (75·7–84·1 months).[15] The patient with laryngeal involvement in this study had severe airway disease requiring a tracheostomy, radiotherapy and laser therapy to the airways which may explain the relatively short overall survival in this case. The other two cases are more complex; lymph node amyloidosis is almost always a complication of low grade lymphoma suggesting that this case was a form of PTLD. Localised gastrointestinal amyloid can also progress to systemic disease over time and, like lymph node amyloidosis, should be followed up carefully recognising the risk of progression.[15]

This series contains a surprising number of cases of AA amyloidosis. This was unexpected as AA amyloidosis is a rare condition, with an estimated incidence of one to two cases per million person-years.[16] Possible explanations for this finding include that AA amyloidosis was established but undiagnosed at the time of the solid organ transplant, i.e. was the unidentified cause of end stage renal failure. Against this, two of the 11 patients were recipients of a heart transplants (an organ rarely affected by AA type amyloid), and also the cause of end stage organ failure was established in 5/11 of the AA cases (eosinophilic granulomatosis with polyangiitis, 2 hypertensive nephropathy, mesangiocapillary glomerulonephritis and reflux nephropathy). Of these diseases only eosinophilic granulomatosis with polyangiitis is likely to be associated with significant ongoing systemic inflammation and a sustained hepatic acute phase response. This implies that AA amyloidosis developed following the solid organ transplant. In five of the 11 patients a chronic

inflammatory condition was identified (bronchiectasis 2, gout with hepatitis B, recurrent infections and tuberculosis with an aspergilloma). In three patients the cause of chronic inflammation was occult, although this is in keeping with the 28% that is quoted in the literature for AA in general,[16] it raises the possibility that long term transplant immunosuppression could predispose patients to either chronic infections or chronic inflammation of undetermined cause. This may explain the poor OS of the 11 AA patients in this study (15 months compared to a median OS of 6-9 years), [16] although immunosuppression might be expected to at least partially control or ameliorate a number of commoner inflammatory conditions.

The development of AL amyloidosis in the post-transplant setting is less surprising as it is a potential complication of PTLD. Systemic AL amyloidosis was found in 14 patients in this series with a further two patients with apparently localised amyloidosis in whom there was plausible concern about indolent lymphoma. This could be an incidental finding, but AL amyloidosis, although about six fold more common than AA amyloidosis, is still vanishingly rare with an incidence of five to twelve people per million person-years.[17]

The detection of a monoclonal gammopathy (MGUS) post-transplant is common, reported to be 10 fold higher than in the dialysis population. [18] Generally, the MGUS is thought to be transient and not increase the risk of developing a PCN or other plasma cell dyscrasias.[7,19] The median age at diagnosis with AL amyloidosis in this study was only 50 years and yet the time from transplantation to a diagnosis of AL amyloidosis was 12 years suggesting that AL amyloidosis maybe a late complication perhaps reflecting an indolent form of PTLD. Without treatment progressive AL

amyloidosis risks graft and eventually other organ failure and death. Outcomes were not favourable with a median OS of 23.5 months and 79% of patients had died or clinically relapsed during the observation period. This compares with a 2012 estimate of median OS of 52 months (95% CI, 48 to 56 months).[20] This presumably reflects the complexity of treating amyloidosis in the presence of a solid organ transplant; patients go into treatment relatively immunosuppressed and with a vulnerable graft which often has a limited functional reserve. Chemotherapy is of no benefit in other types of amyloidosis and the considerable treatment associated risks highlight the importance of definitive diagnosis of amyloid type and extent before embarking on treatment.

This study has a number of limitations; it is a retrospective analysis and, given the rarity of the condition, includes patients collected over a long period resulting in missing data. Details of the immunosuppression taken at the time of diagnosis with amyloidosis were only available in 43% of cases, and any dose modification made to the immunosuppression regimen was lacking. This period was an era of dramatic change in chemotherapy regimens and precludes useful comparison between individuals or published outcomes of twenty-first century treatments.

In conclusion this case series is relatively large suggesting that transplantation is a genuine risk factor in the development of both AL and, strikingly, AA amyloidosis. This has not previously been described in the literature. In AL amyloidosis the most likely explanation is of a subtle PTLD[3] but the finding of 11 cases of AA amyloidosis raises questions about the extent of chronic inflammation in transplant recipients with potential severe consequences.

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