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Clinicopathological Conference Report

Posttransplant IgA Nephropathy: Again and Again and AGAIN?

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HISTORY

Patient reported to Postgraduate Institute of Medical Education and Research (PGIMER) in 2002 with chronic kidney disease wherein basic disease was unknown. He underwent live related renal allograft transplantation (LRRAT) in 2002 where his mother was the donor. However, graft lasted only for 4 years and reported graft loss in 2006, when biopsy was reported as chronic allograft nephropathy.

Second transplant (2006) was again LRRAT and the donor was younger brother using Daclizumab for induction. In 2011 renal dysfunction indicated graft biopsies done were suggestive of cellular and humoral rejection along with recurrent IgA nephropathy and calcineurin inhibitor (CNI) toxicity. He had pulmonary tuberculosis which was treated with antitubercular treatment. However, he lost second graft also. He was on hemodialysis for 3 months when he contracted Hepatitis C virus (HCV) which was treated with sustained virologic response (SVR). Arteriovenous graft also got thrombosed and was excised. He was later put on continuous ambulatory peritoneal dialysis (CAPD). In 2012, he was diagnosed to have vertebral tuberculosis which was treated.

His second graft also failed requiring third transplant in May 2014. This time it was deceased donor renal allograft (DDRAT). The donor was a 34-year-old male victim of road traffic accident. This kidney was placed in right iliac fossa intraperitoneally and anastomosed to iliac vessels. Induction was given [antithymocyte globulin (ATG), followed by cyclosporine/mycophenolate mofetil (CSA/MMF)/prednisolone]. He was noticed to have anterior urethral stricture intraoperatively. Optical internal urethrotomy (OIU) was done followed by advise for self-calibration.

In December 2015, he developed *Escherichia coli* graft pyelonephritis, dialysis requiring acute graft dysfunction which recovered. Serum creatinine on follow-up was 1.8 mg/dL. In February 2016, he developed anasarca and 24-hour urine protein was 8.3 gm with serum albumin of 2.4g/dL and serum creatinine of 2.8 mg/dL. Graft biopsy done showed crescentic IgA nephropathy with evidence of antibody-mediated rejection for which he received therapeutic plasma exchange (TPE) with intravenous immunoglobulin (IVIG), pulse methyl prednisolone followed by 1 mg/kg prednisolone and cyclophosphamide pulse.

In March 2016, he was admitted with odynophagia, painful lip ulcers of 10 days duration, nonproductive cough, and dyspnea on exertion of 4 days duration. On examination, he was conscious, oriented, pale with no icterus, cyanosis, lymphadenopathy, clubbing or edema noted. There was lower lip ulcer+, crusting+, tender ulcers with white base on uvula and palatal arch. Two pustules over left side of neck seen. One pustule over forehead. Multiple swellings over left arm and cubital area were found. Afebrile, pulse rate (PR): 120/minute, BP: 130/80 mm Hg, SpO_2: 98% on room air, RR: 20/minute. Per abdomen examination revealed soft abdomen, tenderness present in right hypochondrium, and right iliac region on deep palpation. Multiple surgical scars were present. Respiratory system revealed left infrascapular crackles. CVS: Tachycardia, S1S2 normal, no murmurs. CNS: Conscious, oriented, bilateral severe sensorineural hearing loss. No other focal neurological deficits noted.

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	17/3	18/3	23/3
Hb	7.8	7.8	6.5
Plt($\times 10^3$)	125	130	128
TLC	7500	6700	17300
DLC			95/1/3/1
Reticulocyte			
MCV			84
MCH			26
MCHC			31.1

	18/3	22/3
pH	7.35	7.26
pO_2	30	60.2
pCO_2	20.5	17
$cHCO_3$	11.1	7.3
SO_2	49	84.2

	17/3	18/3	19/3	20/3	22/3
Na/K	130/6.8	135/5.82	138/5.1	141/5.6	137/5.7
Urea/Crea	263/4.5	270/4.8	245/4.5	249/4.4	255/5
Bilirubin	0.1	0.22			0.06
AST		16			15
ALT		13			11
ALP		92			122
T. protein		5.4	5.6		5.3
S. albumin		2.5	2.5		2.2
Ca/Mg		9.2	8.6/1.5		6.6/1.7

Urine for decoy cells: positive (February 16)
Blood BKV DNA PCR: <100 copies/mL
Urine RE (21/3/16): Sugar: 3+ Albumin: 3+ Microscopy: NAD
Serum procalcitonin (18/3/16): 3.2 Blood c/s (17/3/16): sterile
Swab from pharyngeal wall (17/3/16): *Staphylococcus aureus* sensitive to methicillin
Urine C/s (19/3/16): *E. coli* sensitive to gentamicin, amikacin, norfloxacin, nitrofurantoin.
CKMB (21/3/16): 78 CMV DNA PCR: 32.4×10^5 copies/mL
Course in hospital: Keeping the possibilities of herpes labialis, pharyngeal, and esophageal candidiasis, the patient was started on acyclovir, fluconazole, and topical nystatin. Upper gastrointestinal (GI) endoscopy was done which was suggestive of grade C esophagitis with one punched out ulcer with clean base. Cytomegalovirus (CMV) DNA polymerase chain reaction (PCR) was done, which showed 32.4×10^5 copies/mL. Started on i.v. gancyclovir from 21st March 2016. In view of furuncles and pharyngeal swab growing *Staphylococcus aureus*, he was started on oral amoxicillin/clavulanate. Patient was afebrile during hospital course, and ulcers showed clearing of slough and started accepting orally. Developed chest pain on 21st March 2016. On evaluation ECG was normal with negative Troponin T test and normal CKMB levels. Chest X-ray was done which showed "a suspicious cavity." High-resolution computed tomography (HRCT) done next day on multifocal areas of consolidation with cavitation and nodules and surrounding ground glass opacities. On 22nd March 2016 evening, had high sugars with raised serum ketones and arterial blood gas analysis showed pH of 7.258, cHCO 7.3. Intravenous insulin and IV fluids were continued but patient became dyspneic and on examination had bilateral basal crepitation. Intravenous fluids were stopped, diuretics were given, and patient was placed in propped up position. Patient passed 1600 mL of urine. He was maintaining saturation of 96% on room air. Over next 30 minutes patient symptomatically improved. Blood sugar had come down to 186 mg/dL at 1 AM and 134 mg/dL at 2 AM. Insulin infusion was stopped. At 4.30 AM on 23rd March 2016 patient suddenly became dyspneic, leading on to gasping in next few minutes. Pulse was not palpable, BP not recordable. Patient developed asystole. Cardiopulmonary resuscitation (CPR) was delivered as per protocol but patient could not be revived and was declared dead at 5 AM on 23rd March 2016.

UNIT DIAGNOSIS

Acute on chronic allograft dysfunction, herpes labialis, oropharyngeal candidiasis, CMV esophagitis, and CMV viremia, Staphylococcal furunculosis, steroid-induced diabetes, DKA, cavitary pneumonia in immunosuppressed 'fungal' bacterial with respiratory failure.

CLINICAL ANALYSIS

This patient had allograft dysfunction reasons for which could be:

- Prior pyelonephritis
- Crescentic IgA
- Antibody-mediated rejection
- BK virus (BKV) tubulointerstitial nephritis
- Hyperglycemia osmotic changes

Biopsy had shown evidence of:

- Recurrent IgA
  - Second graft showed e/o IgA nephropathy
  - Nephrotic range proteinuria
  - Mesangiocapillary pattern of injury
  - 3+ IgA codominant with C3 deposition

However, there was no endocapillary proliferation and there was ptc2 and C4d positivity in ptc, hence in third transplant with multiple blood transfusions with biopsy showing:

- Mesangiocapillary pattern
- Grade 2 peritubular capillaritis
- C4d positivity

- Features were suggestive of antibody-mediated rejection though there was no glomerulitis and status of donor-specific antibody was not known.

Possibility of pyelonephritis and BKV nephropathy is unlikely as a cause of graft dysfunction as there was:

- Bacteriuria but no pyuria
- Decoy cells but blood BKV DNA PCR is negative

For his lung cavitary lesions, the following possibilities are to be considered:

- Bacterial
- Fungal
- Tubercular
- Viral
- Vasculitis
- Immunosuppressed.

Radiologic picture showed nodular infiltrates with halo sign and reverse halo sign and cavitation, suggestive of angioinvasive fungal infection.

The following investigations could have helped, however, were not done:

- Galactomannan, Beta D glucan
- Broncho alveolar lavage
- Pneumocystis – cotrimoxazole prophylaxis

Tuberculosis is an important differential diagnosis in this immunosuppressed setting. Points in favor being

- Endemic area
- Prior h/o tuberculosis
- Posttransplant high relapse rate
- Radiological features
- Consolidation
- Nodules
- Cavitation
- Supportive evidence could have been from BAL AFB PCR.

Viral pneumonia – Herpes, CMV can also be considered with evidence of active infection, i.e., CMV viremia or Herpes labialis, however cavitation would be very odd.

Cardiovascular involvement could be in the form of:

- Left ventricular hypertrophy
  - ECG evidence
  - Longstanding hypertension
- Valvular heart disease
  - No murmur
  - No IE evidence – lack of peripheral signs, blood C/s sterile
- Myocardial infarction
  - Serial ECG no ST_T changes
- Cardiac arrhythmia

GIT involvement is evident as

Herpes labialis

- Esophagitis
- Hepatitis C (treated)
- Abdominal wall hernia

Etiology for esophagitis could be

Herpes

- Labial infection
- Resolution with acyclovir
- Punched out ulceration

CMV

- Supported by viremia
- But unlikely as there is
  - No leucopenia
  - No hepatitis
  - Linear ulceration typically
  - IHC negative

Candida – Oral thrush

So, anticipated sequence of events are:

- Crescentic IgAN + ABMR
- High dose steroids and cyclophosphamide
- Steroid induced diabetes
- CMV, herpes, staphylococcal cutaneous infection, candidiasis
- Pneumonia-fungal polymicrobial
- Worsening hypoxemia
- Cardiac arrest

Final Clinical Diagnosis

- Basic disease: IgA nephropathy
- Prior twice graft loss
- DDRT May 2014
- Crescentic IgA
- Antibody-mediated rejection
- Steroid induced diabetes – Diabetic keto acidosis
- CMV viremia
- Herpes labialis, esophagitis
- Cavitary pneumonia – angioinvasive fungal.

CLINICAL DISCUSSION

Dr Sahajal – As far as pulmonary radiology is concerned, reverse CT halo sign is more common in Mucormycosis, hence I shall favor Mucormycosis.

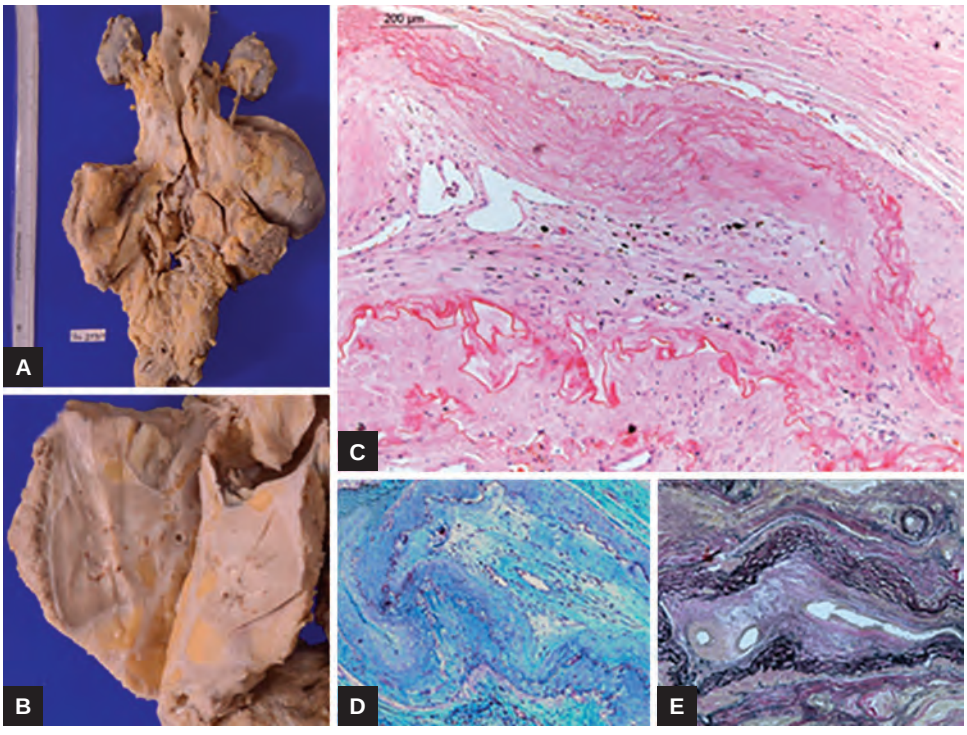
Dr Manish Rathi – In this immunocompromised patient with diabetic ketoacidosis, we expect multiple infections in autopsy, including viruses.

Dr Chakraborty – I agree with Dr Sahajal. Mucormycosis also shows multiple nodules in lungs as seen in this case. Galactomannan serology can resolve Aspergillus *vs* Mucormycosis debate.

Pathology Protocol – Professor Ritambhra Nada

Antemortem Biopsies Reports

1st Transplant: 8503/02 – acute cellular rejection, 12037/04 – FSGS' IgA, 7279/06 – CAN



Figs 1A to E: (A) Gross photograph of two native and three graft kidneys; (B) gross photograph showing cut surface of graft kidney with atrophied cortex and indistinct corticomedullary junction; and (C to E) sections showing obliterative arteritis in graft kidney (H&E, Masson's trichrome, Elastic van Gieson stain)

2nd Transplant: 10381/06 (zero hour) normal, 12393/06 – ACR +ABMR, 15263/06 – ACR+ABMR, 2912/07 (protocol 6 months) normal, 7151/08 – CAN + ABMR
3rd Transplant: 11101/14 – CNI + ATN, 2576/16 – ABMR + Crescentic IgA.

Kidneys; native kidneys (80 gm) were small shrunken with increased intrapelvic fat. Microscopic examination showed chronic glomerulonephritis with thyroidization of tubules, arterionephrosclerosis and cortical adenomas (Figs 1A to E).

1st Transplant: Kidney was small fibrotic. Microscopic examination showed complete sclerosis of glomeruli, marked tubular loss in cortex and medulla, obliterative recanalized thrombi with evidence of arteritis.

2nd Transplant: Small shrunken kidney which on microscopy showed complete sclerosis of glomeruli with fibrous crescents, marked tubular loss in cortex and medulla, obliterative recanalized thrombi with evidence of arteritis.

3rd Transplant: Pale enlarged kidney (120 gm), anastomotic sites were patent. Microscopic examination showed IgA nephropathy, crescentic glomerulonephritis with mesangiocapillary pattern, focal collapse and tubulitis with PTC dilatation and margination, hyaline arterionephrosclerosis and transplant arteriopathy (Figs 2A to I).

The overall features are of IgA nephropathy with ABMR and ACR with arteritis and transplant arteriopathy with superimposed thrombosis.

Renal biopsies and histology at autopsy confirms presence of recurrent IgA nephropathy with evidence of thrombotic tendency in multiple graft indicating presence of some genetic predisposition for both the events.

Lungs (1090 gm): Showed multiple hemorrhagic infarcts and nodules with areas of consolidation. There was no evidence of tuberculosis. Microscopic examination confirmed hemorrhagic infarcts, pneumonitis with invasive Mucormycosis and Aspergillosis. There was no evidence of tuberculosis (Figs 3A to D).

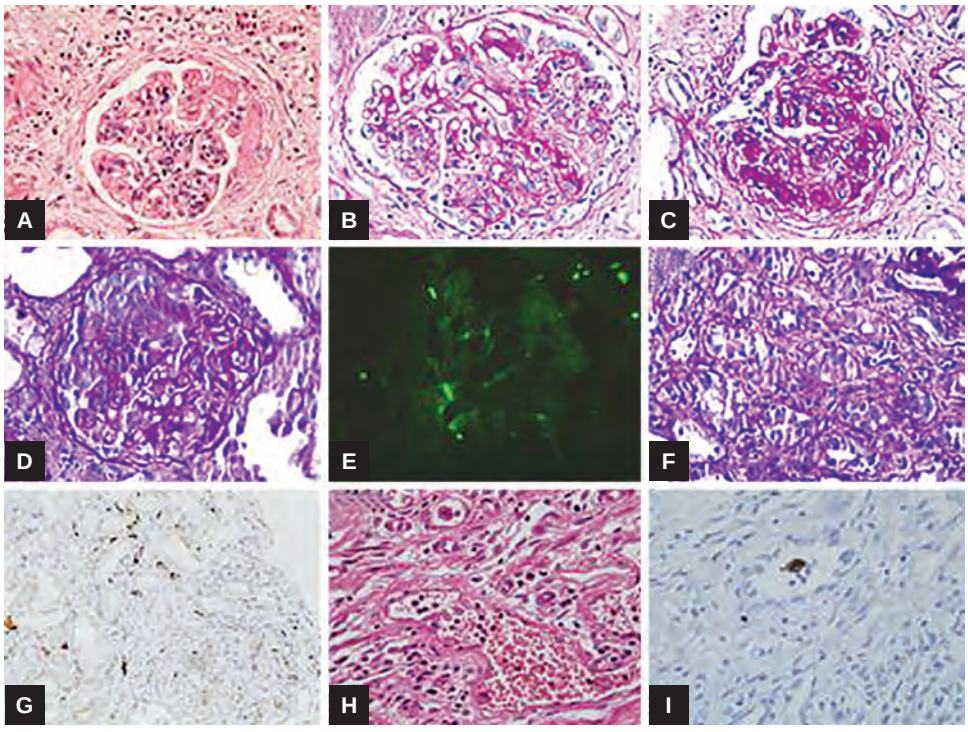
Liver (100 gm): Gross and microscopic examination of the liver was normal.

Spleen (550 gm): Gross examination of spleen was normal and microscopy examination revealed white pulp depletion. There was no evidence of infection.

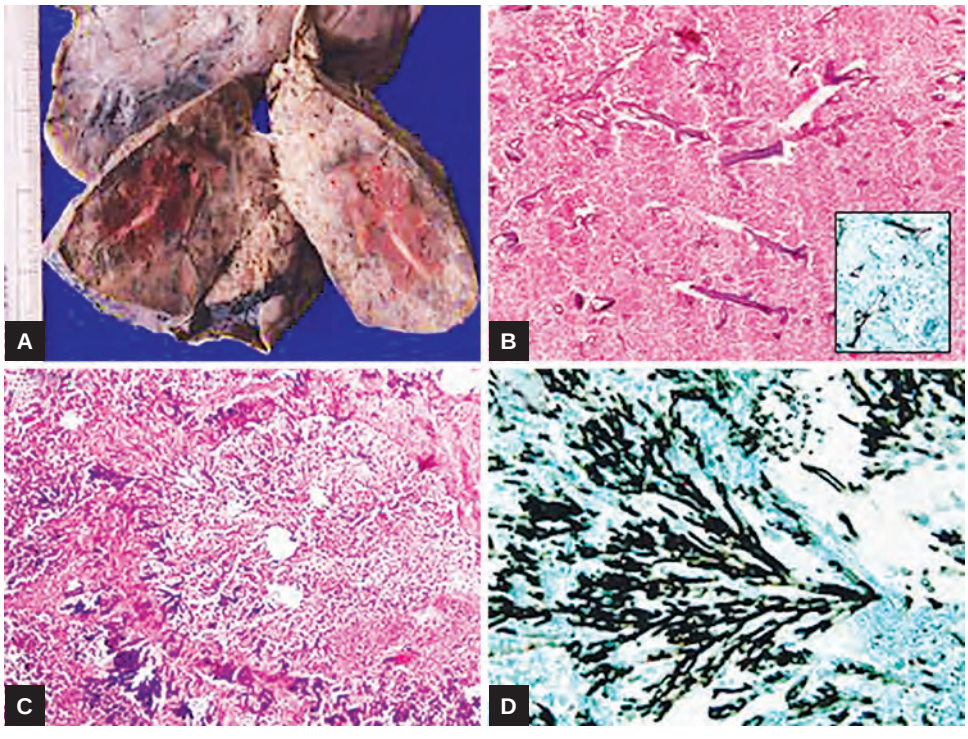
GIT: Lower end of the esophagus showed discrete linear ulcers (1.5 cm). Histopathologic examination confirmed the ulcers. Endothelial cells and macrophages at bases of these ulcers showed CMV inclusions which were confirmed by immunohistochemistry.

Pancreas did not reveal any gross pathology. However, on histology, it showed changes in arteries which showed intimal proliferation with ectasia. Adjacent parenchyma showed mild interstitial fibrosis.

Heart (220 gm) showed uremic pericarditis whereas chambers and valves were normal. Coronary arteries also showed ectasia with intimal proliferation.



Figs 2A to I: (A to C) Photomicrograph showing varying aged crescents and underlying tuft showing mesangiocapillary pattern of injury (H&E and PAS stain); (D) PAS stained section showing collapse of capillary tuft with podocytic hyperplasia; (E) direct immunofluorescence photomicrograph showing 2+ fine granular mesangial and capillary loop positivity for IgA; (F) PAS stained section showing peritubular capillary dilatation and margination; (G) immunohistochemistry for C4d showing linear continuous positivity in peritubular capillaries; (H) section from esophageal ulcer showing CMV inclusions in endothelial cells of granulation tissue; and (I) immunohistochemistry for CMV confirming the same



Figs 3A to D: (A) Gross photograph of lung showing hemorrhagic infarct; (B) section from infarcted region showing mucor (H&E stain, inset Grocott's stain); and (C and D) section showing invasive pulmonary aspergillosis (H&E and Grocott's stain)

FINAL AUTOPSY DIAGNOSIS (PM 27317)

Live Related (TWICE) and Cadaveric Multiple Renal Graft Recipient

Native kidneys – Chronic glomerulonephritis, cortical adenomas

1st Transplant – IgA nephropathy with chronic glomerulonephritis, interstitial fibrosis with tubular loss, transplant arteriopathy with recanalized thrombi

2nd Transplant – IgA nephropathy with chronic glomerulonephritis, interstitial fibrosis with tubular loss, transplant arteriopathy with recanalized thrombi

3rd Transplant – IgA crescentic glomerulonephritis, C4d positive antibody-mediated rejection and transplant arteriopathy

Arteriopathy in coronary and pancreatic arteries with focal ischemia

Lungs – Invasive mucormycosis and aspergillosis, hemorrhagic infarcts and pneumonitis

CMV esophagitis

FINAL AUTOPSY DISCUSSION

Dr Valliapan – Could the arteritis outside kidney be medium vessel vasculitis or immunological process?

Dr Nada – Whether rejection can extend beyond renal vessels is unanswered. Pancreatic arteries and coronaries did show endothelial activation but rejection process should restrict to immunologically activated organ.

Dr Ashish Sharma – Arteritis outside kidney is unlikely to be an immunological process as antigens on other vessels are different from those in kidneys.

Dr Manish Rathi – The arteritis is unlikely to be an immune-related vasculitis. It could be infection-related vasculitis that requires heavy immunosuppression for management. Can we show IgA deposition in native kidneys?

Dr Nada – Native kidneys are totally sclerosed, and it was not possible to show immunoglobulin deposition on immunofluorescence.

Dr Chugh – IgA nephropathy is very common in Asia. The most important lesson is that, IgA nephropathy has a subset which can recur in graft kidney in a short period.

Dr Jindal – How many transplants in an individual patient have been done?

Dr Venkat – Up to 5 transplants have been done in a single patient.

Dr Nada – IgA nephropathy generally recurs in 3 years. In this case it progressed faster. It came back in three grafts with evidence of recanalized thrombi, suggesting a possibility of genetic predisposition.

Dr Ashish – In such a setting with recurrent disease, if we increase immunosuppression then patient acquires infection and we have to give up on graft at some point depending on clinical scenario. What is the cause of heavy protienuria in this crescentic disease.

Dr Nada – The collapse is responsible for 8 gm proteinuria and not crescents.

Dr Venkat – While treating IgA nephropathy recurrence, the outcome is poor. We should give prophylaxis for infection.

Dr Nada – IgA nephropathy with C3 deposits on immunofluorescence are likely to have genetic abnormality, so genetic work up of alternate pathway should be considered before transplant.

Dr Sehjal – Lung infection seems to be difficult to salvage in this case. A lobectomy with amphotericin B injections could be a possibility.

SUMMARY

IgA nephropathy is one of the commonest glomerulonephritis to recur after renal transplant. The incidence of recurrence ranges from 9 to 61% and usual time of recurrence is 3 years. Recurrence has been described to be more frequently associated with younger age at diagnosis, faster progression to ESRD, HLA B8 and DR3 and related donors. The factors associated with early recurrence are undetermined. It has been reported that the presence of C3 deposits on DIF in cases of IgA nephropathy are associated with novel N terminal mutation in Factor H. In these cases, it is possible that the disease may recur faster in allografts. The cause for arteritis in coronary and pancreatic vessels is uncertain.

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