ΚΛΙΝΙΚΟ ΦΡΟΝΤΙΣΤΗΡΙΟ ΜΕ ΘΕΜΑ:

«ΜΕΤΑΜΟΣΧΕΥΣΗ ΝΕΦΡΟΥ:
ΑΠΟ ΤΟΝ ΠΡΟΜΕΤΑΜΟΣΧΕΥΤΙΚΟ ΕΛΕΓΧΟ
ΣΤΗ ΜΕΤΑ-ΜΕΤΑΜΟΣΧΕΥΤΙΚΗ ΠΑΡΑΚΟΛΟΥΘΗΣΗ»

ΙΣΤΟΠΑΘΟΛΟΓΙΑ ΝΕΦΡΙΚΟΥ ΜΟΣΧΕΥΜΑΤΟΣ

Χριστίνα Βουρλάκου
Παθολογοανατομικό Τμήμα ΓΝΑ ‘’Ο Ευαγγελισμός’’

Θεραπευτήριο: "Ευαγγελισμός"

ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
Ο ΕΥΑΓΓΕΛΙΣΜΟΣ

ΙΣΤΟΠΑΘΟΛΟΓΙΑ ΝΕΦΡΙΚΟΥ ΜΟΣΧΕΥΜΑΤΟΣ

Η εξέλιξη στην μεταμόσχευση νεφρού απαιτεί βελτίωση της κατανόησης και της εκτίμησης της απόρριψης και της νεφρικής βλάβης σε ιστολογικό επίπεδο.

1. Κυτταρικού τύπου απόρριψη [T cell-mediated rejection (TCMR)]
2. Απόρριψη με την μεσολάβηση αντισωμάτων [Antibody-mediated rejection (ABMR)]
3. Οξεία Νεφρική βλάβη [Acute kidney injury (AKI)]
4. Ατροφία σωληναρίων & Διάμεση Ίνωση [Tubular atrophy and interstitial fibrosis]

TCMR & ABMR: Μοιράζονται τα αποτελέσματα με τη μεσολάβηση της IFN γ

TCMR: Έχει προκύψει ως συγγενής διαδικασία του Τ-κυττάρου που παρουσιάζει το αντιγόνο στον διάμεσο ιστό

ABMR: Αποτελεί διαδικασία με την μεσολάβηση φυσικών κυττάρων-δολοφόνων που συμβαίνει στην μικροκυκλοφορία & είναι η κύρια αιτία της αποδιοργάνωσης του μοσχεύματος

Πρόσφατα η σχέση μεταξύ έκφρασης γονιδίων και κλινικών φαινοτύπων οδήγησε στην ανάπτυξη ενός συστήματος που καθιστά δυνατή τη διάγνωση συγκεκριμένων νοσημάτων με βάση τα επίπεδα **mRNA**

Οι μοριακές μεταβολές που σχετίζονται με τη νεφρική βλάβη είναι συχνά πιο εκτεταμένες από τις προτεινόμενες από την ιστολογία και υποδεικνύουν ότι η δυσλειτουργία του μοσχεύματος προκαλείται από συνεχή βλάβη των νεφρώνων παρά από την ίνωση.

Η μοριακή αξιολόγηση της νόσου έχει βελτιώσει την κατανόηση των συγκεκριμένων διεργασιών που εμπλέκονται στην έκβαση του μοσχεύματος

The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology

American Journal of Transplantation 2017; 17: 28–41
Wiley Periodicals Inc.

The goal of the Banff process is ongoing integration of advances in histologic, serologic, and molecular diagnostic techniques to produce a consensus-based reporting system that offers precise composite scores, accurate routine diagnostics, and applicability to next-generation clinical trials.

The XIII Banff meeting was held October 5–10, 2015, in Vancouver, Canada, in conjunction with the annual meeting of the Canadian Society of Transplantation.

The XIV Banff meeting was held jointly with the Catalan Society of Transplantation in Barcelona, Spain, March 27–31, 2017

Updated 2015 Banff classification categories

Category 1: Normal biopsy or nonspecific changes

Category 2: Antibody-mediated changes

- **Acute/active ABMR** [Antibody-mediated rejection]
- **Chronic active ABMR**
- **C4d staining without evidence of rejection**

Category 3: Borderline changes Suspicious for acute TCMR

Category 4: TCMR [T cell-mediated rejection]

- **Acute TCMR**
- **Chronic active TCMR**

Category 5: Interstitial fibrosis and tubular atrophy

Category 6: Other changes not considered to be caused by acute or chronic rejection

Updated 2015 Banff classification categories

Category 1: Normal biopsy or nonspecific changes

Category 2: Antibody-mediated changes

Acute/active ABMR All **three features** must be present for diagnosis. Biopsies showing histological features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious for acute/active ABMR. Lesions may be clinically acute or smoldering or may be subclinical; It should be noted if the lesion is C4d-positive or C4d-negative, based on the following criteria:

1. Histologic evidence of **acute tissue injury,** including **one or more** of the following:

- Microvascular inflammation (g >0 in the absence of recurrent or de novo glomerulonephritis, and/or ptc >0)
- Intimal or transmural arteritis (v >0)
- Acute thrombotic microangiopathy in the absence of any other cause
- Acute tubular injury in the absence of any other apparent cause

2. Evidence of **current/recent antibody interaction with vascular endothelium,** including **at least one** of the following:

- Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections or C4d >0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2), although in the presence of acute TCMR, borderline infiltrate, or infection; ptc ≥2 alone is not sufficient, and g must be ≥1
- Increased expression of **gene transcripts** in the biopsy tissue indicative of endothelial injury, if thoroughly validated

3 . Serologic evidence of DSAs (HLA or other antigens)

- Biopsies suspicious for ABMR on the basis of meeting criteria 1 and 2 should prompt expedited DSA testing

Updated 2015 Banff classification categories

Chronic active ABMR All **three features** must be present for diagnosis. As with acute/active ABMR, biopsies showing histological features plus evidence of current/recent antibody interaction with vascular endothelium or DSA, but not both, may be designated as suspicious, and it should be noted if the lesion is C4d-positive or C4dnegative, based on the criteria listed:

1. Histologic evidence of **chronic tissue injury,** including **one or more** of the following:

- TG (cg >0), if no evidence of chronic thrombotic microangiopathy; includes changes evident by EM only (cg1a; Table 4)
- Severe peritubular capillary basement membrane multilayering (requires EM)
- Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of biopsy-proven TCMR with arterial involvement but are not required

2. Evidence of **current/recent antibody interaction with vascular endothelium**, including **at least one** of the following:

- Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2), although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥2 alone is not sufficient and g must be ≥1
- Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated

3. Serologic evidence of DSAs (HLA or other antigens):

- Biopsies suspicious for ABMR on the basis of meeting criteria 1 and 2 should prompt expedited DSA testing

Updated 2015 Banff classification categories

C4d staining without evidence of rejection

All three features must be present for diagnosis

1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections)

2. g = 0, ptc = 0, cg = 0 (by light microscopy and by EM if available), v = 0; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this)

3. No acute cell-mediated rejection (Banff 1997 type 1A or greater) or borderline changes

Updated 2015 Banff classification categories

Category 3: Borderline changes Suspicious for acute TCMR

- Foci of tubulitis (t1, t2, or t3) with minor interstitial inflammation (i0 or i1) or interstitial inflammation (i2, i3) with mild (t1) tubulitis; retaining the i1 threshold for borderline from Banff 2005 is permitted although this must be made transparent in reports and publications

- No intimal arteritis (v = 0)

Updated 2015 Banff classification categories

Category 4: TCMR

Acute TCMR Grade IA. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of moderate tubulitis (t2)

IB. Significant interstitial inflammation (>25% of nonsclerotic cortical parenchyma, i2 or i3) and foci of severe tubulitis (t3)

IIA. Mild to moderate intimal **arteritis** (v1) with or without interstitial inflammation and tubulitis

IIB. Severe intimal arteritis comprising >25% of the luminal area (v2) with or without interstitial inflammation and tubulitis

III. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

Chronic active TCMR Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neointima); note that such lesions may represent chronic active ABMR as well as TCMR; the latter may also be manifest in the tubulointerstitial compartment

Updated 2015 Banff classification categories

Category 5: Interstitial fibrosis and tubular atrophy
Grade I. Mild interstitial fibrosis and tubular atrophy (≤25% of cortical area)
II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
III. Severe interstitial fibrosis and tubular atrophy (>50% of cortical area)

Category 6: Other changes not considered to be caused by acute or chronic rejection
BK virus nephropathy
Posttransplant lymphoproliferative disorders
Calcineurin inhibitor nephrotoxicity
Acute tubular injury
Recurrent disease
De novo glomerulopathy (other than transplant glomerulopathy)
Pyelonephritis
Drug-induced interstitial nephritis

Banff lesion grading system

Lesions

Quantitative criteria for inflammation: i score

i0 No inflammation or in <10% of unscarred cortical parenchyma
i1 Inflammation in 10–25% of unscarred cortical parenchyma
i2 Inflammation in 26–50% of unscarred cortical parenchyma
i3 Inflammation in >50% of unscarred cortical parenchyma

Quantitative criteria for tubulitis: t score

t0 No mononuclear leukocytes in tubules
t1 Foci with one to four leukocytes per tubular cross-section (or 10 tubular cells)
t2 Foci with five to 10 leukocytes per tubular cross-section (or 10 tubular cells)
t3 Foci with >10 leukocytes per tubular cross-section or the presence of two or more areas of tubular basement membrane destruction accompanied by i2/i3 inflammation and t2 elsewhere

Quantitative criteria for intimal arteritis: v score

v0 No arteritis
v1 Mild to moderate intimal arteritis in at least one arterial cross-section
v2 Severe intimal arteritis with at least 25% luminal area lost in at least one arterial cross-section
v3 Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel

Quantitative criteria for glomerulitis: g score

g0 No glomerulitis
g1 Glomerulitis in <25% of glomeruli
g2 Segmental or global glomerulitis in 25–75% of glomeruli
g3 Glomerulitis in >75% of glomeruli

Quantitative criteria for peritubular capillaritis: ptc score

ptc0 At least one leukocyte in <10% of cortical PTCs and/or maximum number of leukocytes <3
ptc1 At least one leukocyte cell in ≥10% of cortical PTCs with three or four leukocytes in most severely involved PTC
ptc2 At least one leukocyte in ≥10% of cortical PTCs with five to 10 leukocytes in most severely involved PTC
ptc3 At least one leukocyte in ≥10% of cortical PTCs with >10 leukocytes in most severely involved PTC

Quantitative criteria for total inflammation: ti score

ti0 No or trivial interstitial inflammation (<10% of total cortical parenchyma)
ti1 10–25% of total cortical parenchyma inflamed
ti2 26–50% of total cortical parenchyma inflamed
ti3 >50% of total cortical parenchyma inflamed

Banff lesion grading system

Quantitative criteria for inflammation in area of interstitial fibrosis and tubular atrophy: i-IFTA score

i-IFTA0 No inflammation or <10% of scarred cortical parenchyma

i-IFTA1 Inflammation in 10–25% of scarred cortical parenchyma

i-IFTA2 Inflammation in 26–50% of scarred cortical parenchyma

i-IFTA3 Inflammation in >50% of scarred cortical parenchyma

Quantitative criteria for C4d score

C4d0 No staining of PTCs (0%)

C4d1 Minimal C4d staining (>0 but <10% of PTCs)

C4d2 Focal C4d staining (10–50% of PTCs)

C4d3 Diffuse C4d staining (>50% of PTCs)

Quantitative criteria for double contour: cg score

cg0 No GBM double contours by light microscopy or EM

cg1a No GBM double contours by light microscopy but GBM double contours (incomplete or circumferential) in at least three glomerular capillaries by EM, with associated endothelial swelling and/or subendothelial electron-lucent widening

cg1b Double contours of the GBM in 1–25% of capillary loops in the most affected nonsclerotic glomerulus by light microscopy; EM confirmation is recommended if EM is available

cg2 Double contours affecting 26–50% of peripheral capillary loops in the most affected glomerulus

cg3 Double contours affecting >50% of peripheral capillary loops in the most affected glomerulus

Quantitative criteria for mesangial matrix expansion: mm score

mm0 No more than mild mesangial matrix increase in any glomerulus

mm1 At least moderate mesangial matrix increase in up to 25% of nonsclerotic glomeruli

mm2 At least moderate mesangial matrix increase in 26–50% of nonsclerotic glomeruli

mm3 At least moderate mesangial matrix increase in >50% of nonsclerotic glomeruli

Molecular lesions and their corresponding histologic lesions

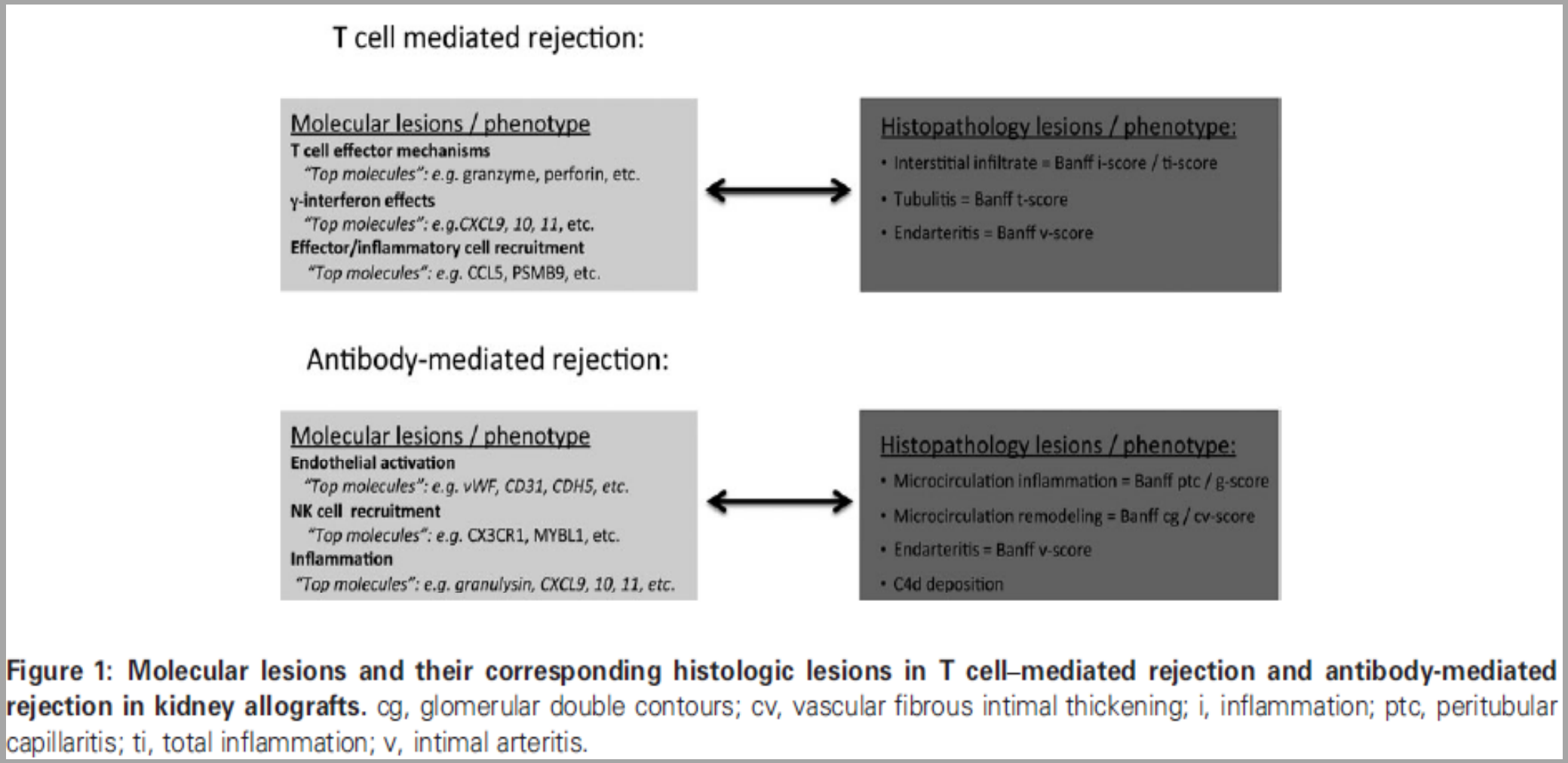
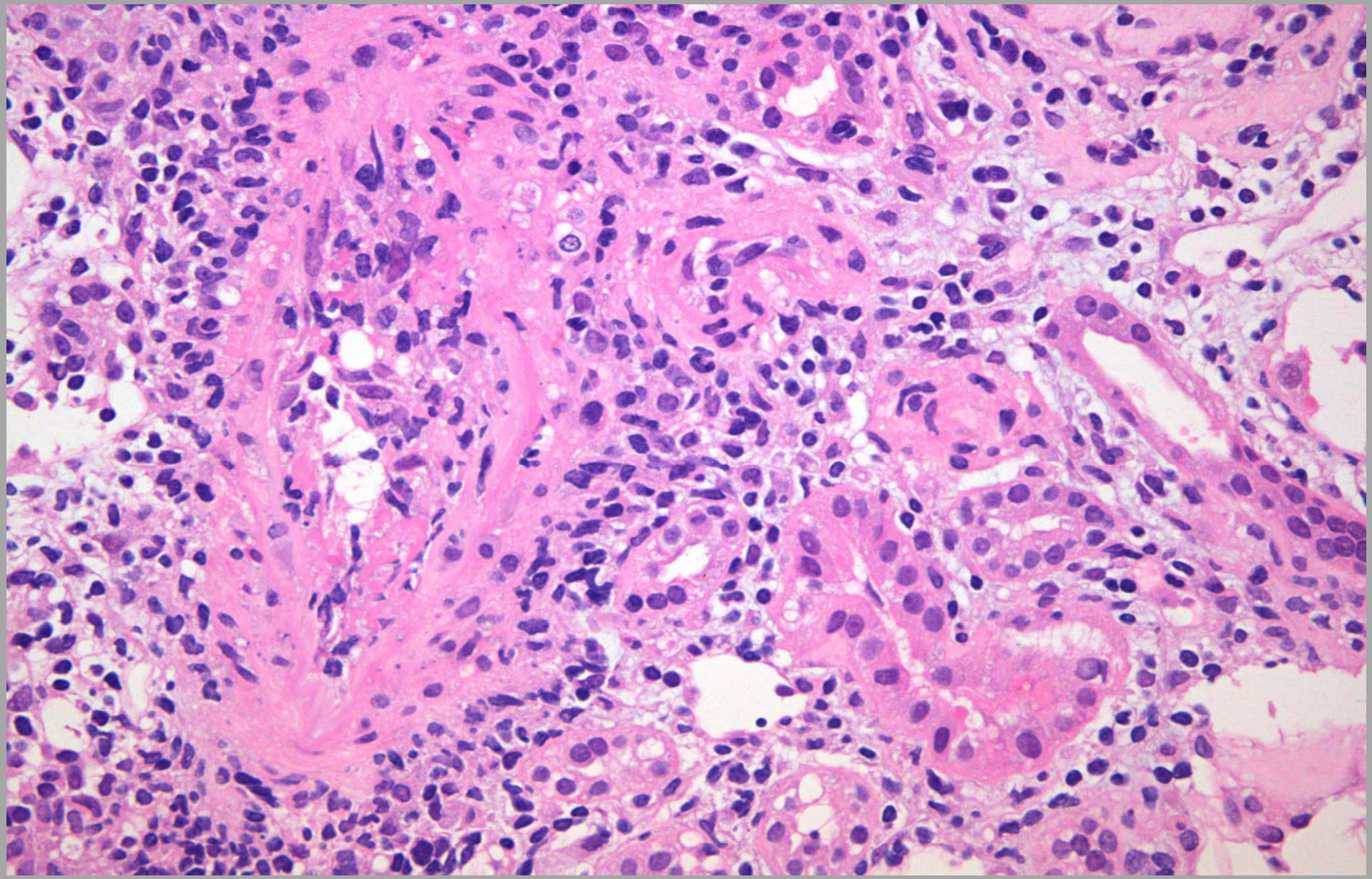
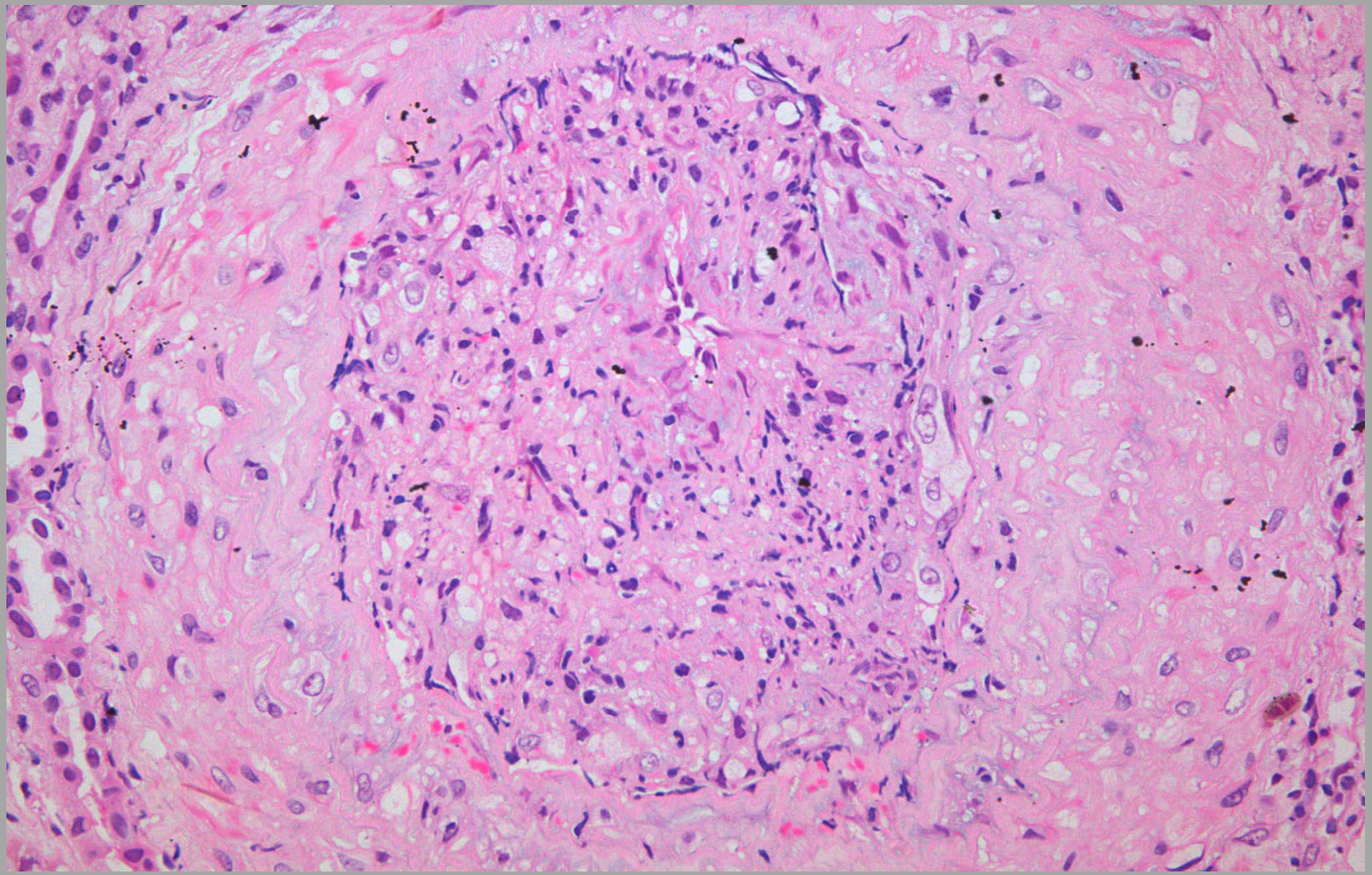


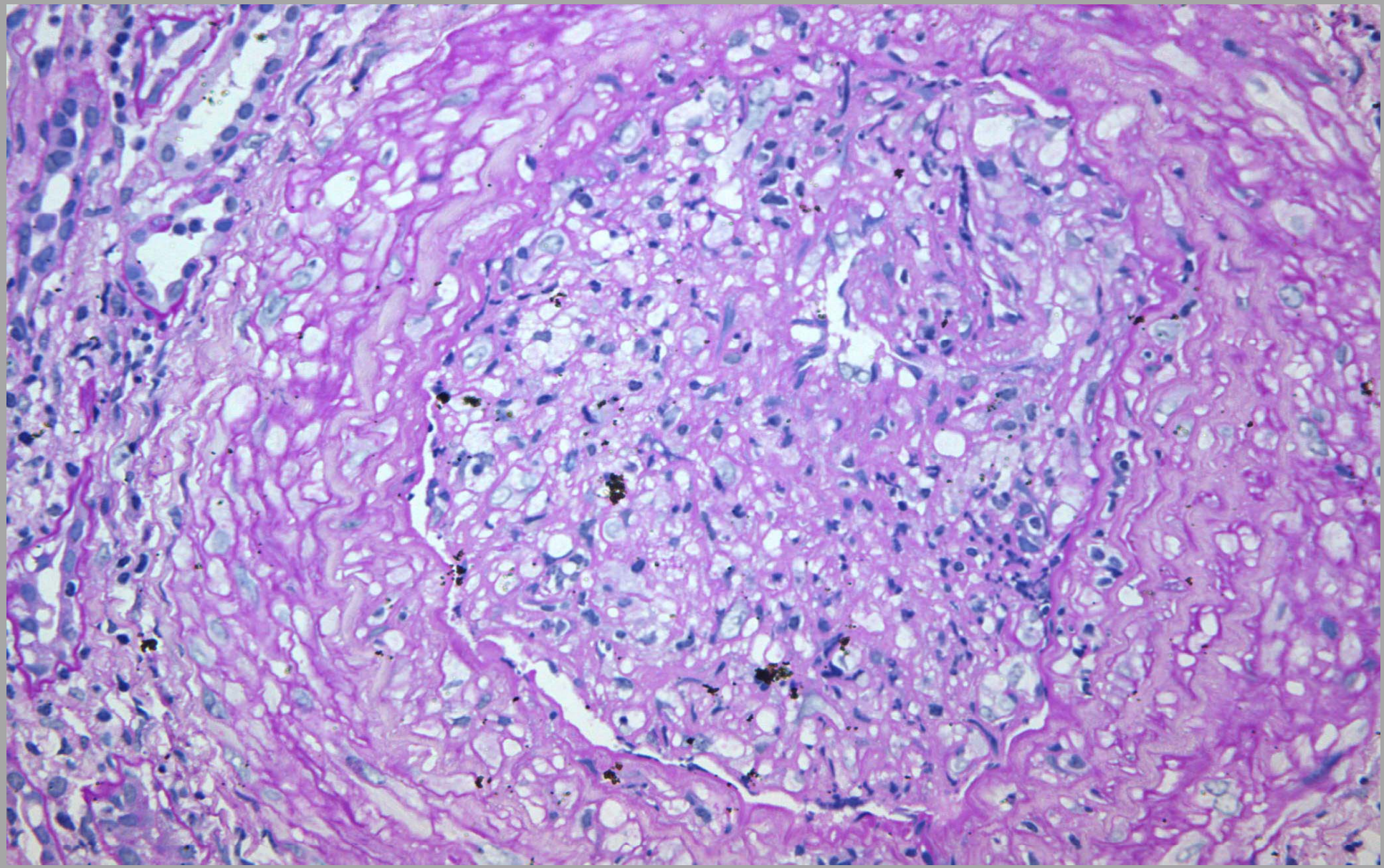
Figure 1: Molecular lesions and their corresponding histologic lesions in T cell–mediated rejection and antibody-mediated rejection in kidney allografts. cg, glomerular double contours; cv, vascular fibrous intimal thickening; i, inflammation; ptc, peritubular capillaritis; ti, total inflammation; v, intimal arteritis.



Acute T- cell-immune mediated rejection / Banff category 4, type 2 rejection / transplant endarteritis



Acute T- cell-immune mediated rejection / Grade Banff 4IIB



Acute T- cell-immune mediated rejection /

Grade Banff 4II

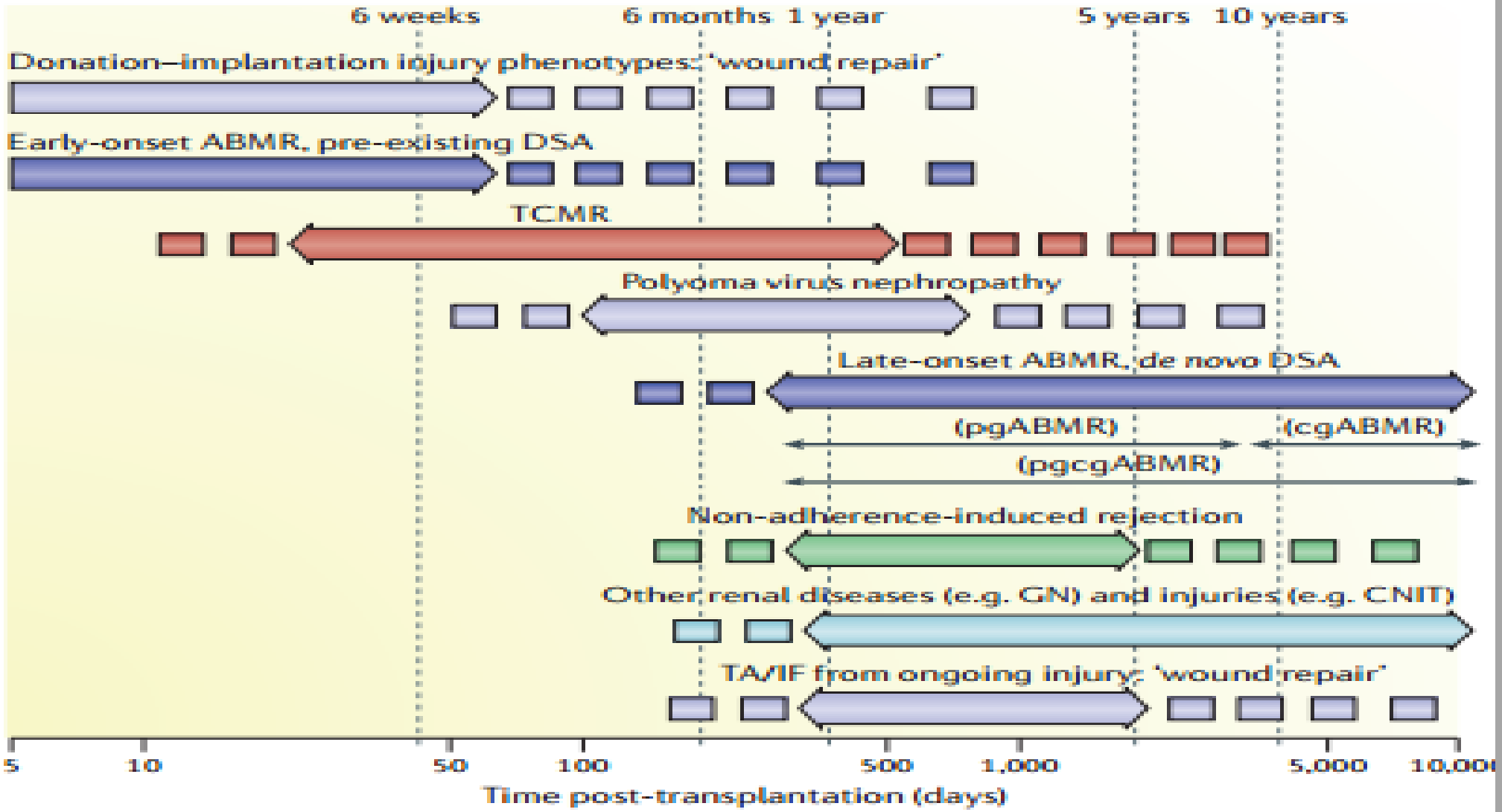


Figure 3 | **Time-dependent effects on disease states after transplantation.** Analysis of the relationship between time post-transplantation to injury caused by the process of donation and implantation, rejection and tubular atrophy and interstitial fibrosis (TA/IF) reveals early (6 weeks to 6 months), intermediate (6 months to 5 years) and late events (>5 years). ABMR, antibody mediated rejection; cgABMR, ABMR with chronic glomerulopathy; CNIT, calcineurin inhibitor toxicity; DSA, donor specific antigen; GN, glomerulonephritis; pgABMR, ABMR with peritubular capillaritis and glomerulitis; pgcgABMR, ABMR with peritubular capillaritis and glomerulitis plus chronic glomerulopathy[78]; TCMR, T cell-mediated rejection.


ΕΥΧΑΡΙΣΤΟΥΜΕ ΠΟΛΥ
ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ
ΣΑΣ