

腎移植認定医第6回集中セミナー 第47回 日本臨床腎移植学会 3/14/2014

3. カテゴリー:免疫抑制 移植腎病理と最新Banff分類

<http://cybernephrology.ualberta.ca/Banff/>



The Banff Conferences on Allograft Pathology 1991 - Present

[Click here for history and general information about the Banff Conferences on Allograft Pathology, the Banff Consensus Process, and Funding.](#)

[Click here to view photos and listen to audio files of the Banff Conference throughout the years.](#)

[Click here for information on the Banff Working Groups.](#)

The Banff Conferences on Allograft Pathology:

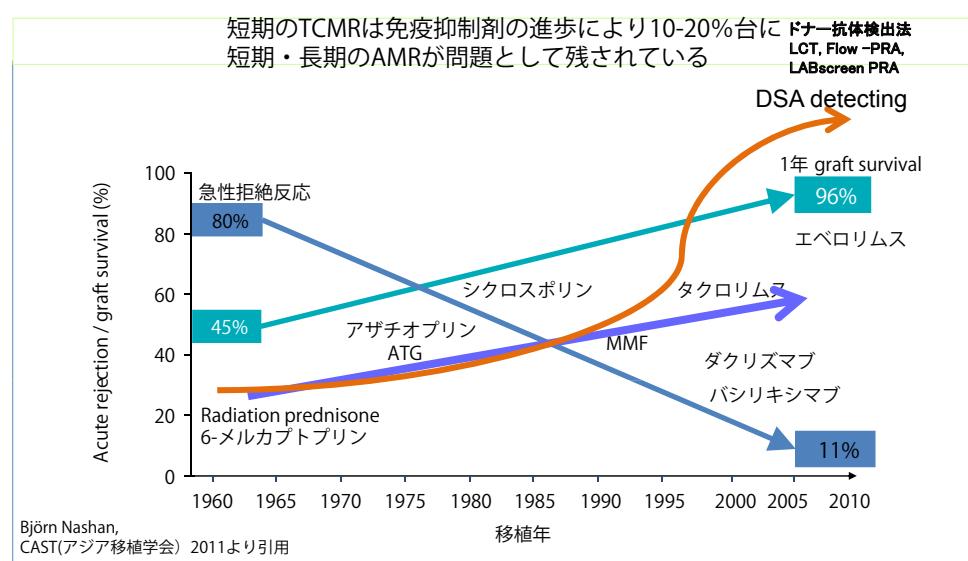
- 1991 The Centre For Conferences - Banff, AB Canada
- 1993 The Centre For Conferences - Banff, AB Canada
- 1995 The Centre For Conferences - Banff, AB Canada
- 1997 The Banff Springs Hotel - Banff, AB Canada
- 1999 The Banff Springs Hotel - Banff, AB Canada
- 2001 The Rimrock Resort Hotel - Banff, AB Canada
- 2003 The University of Aberdeen - Aberdeen, Scotland
- 2005 The Fairmont Hotel Macdonald - Edmonton, AB Canada
- 2007 La Coruña, Spain
- 2009 The Rimrock Resort Hotel - Banff, AB Canada
- 2011 Enghien-les-Bains, France
- 2013 Comendatuba-Bahia, Brazil



Banff 診断に基づいた病理判定

1. Banff classification history & topics
2. Banff classification WG issues
 - BK virus nephropathy
3. non-rejection findings
 - medullary ray injury (MRI)

移植腎長期生着率と免疫抑制薬の進歩



Major Banff classification change

1. clinical definition → immunological definition;
91' → 97'
2. C4d on PTC; 01'
DSA is necessary on diagnosis.
3. CAN → CSAN → IF/TA
91' → 97' → 05'
4. chronic antibody mediated rejection; 05'
chronic T cell mediated rejection
5. isolated v lesion certainly exists.; 07' -13'
C4d negative AMR certainly exists.

Banff code

ti code 2013	i	間質細胞浸潤	0,1,2,3
	t	尿細管炎	0,1,2,3
	v	動脈内膜炎	0,1,2,3
	g	糸球体炎	0,1,2,3
	ptc	PTCits	0,1,2,3
	C4d	PTC or GBM	0,1,2,3
	ci	間質線維化	0,1,2,3
	ct	尿細管萎縮	0,1,2,3
	cv	新生動脈内膜炎	0,1,2,3
	cg	移植糸球体症	0,1,2,3
	ptcbm	PTCBM多層化	0,1,2,3
	mm	メサンギウム基質増加	0,1,2,3
	ah	細動脈硝子化	0,1,2,3

(臨床的)拒絶反応の分類

特集:腎移植 Banff 分類の変遷と最新の話題

武田朝美 両角國男
日腎会誌 2013;55(2):98-101.

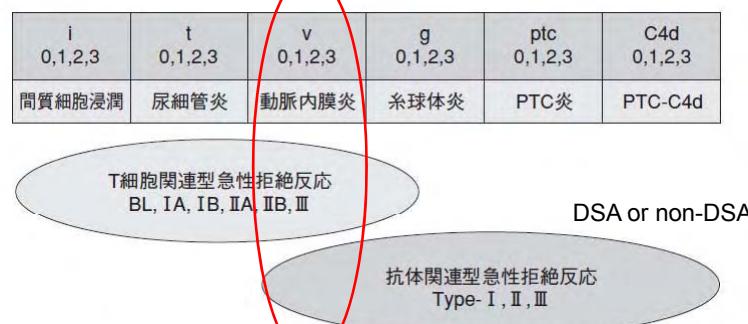
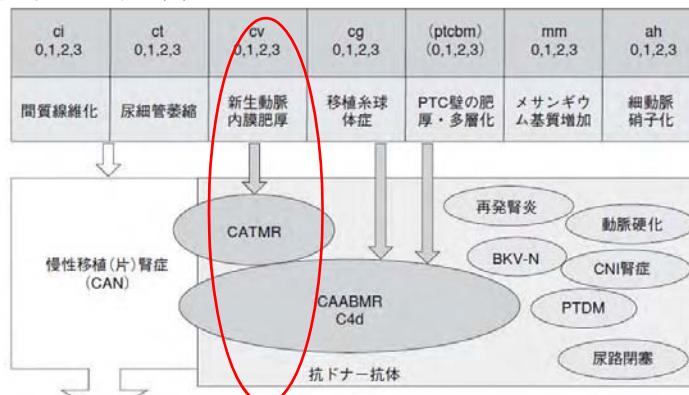
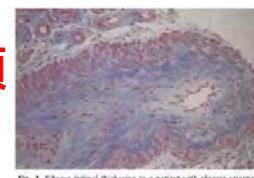


図 1 Banff 分類における急性拒絶反応の病態と各組織病変

(臨床的)拒絶反応の分類

特集:腎移植 Banff 分類の変遷と最新の話題
武田朝美 両角國男
日腎会誌 2013;55(2):98-101.



IF/TA: 非特異的な病変
図 2 Banff 分類における慢性拒絶反応および慢性移植(片)腎症の位置づけ

Banff classification							Banff 2007
BL.	,2,3	0,	v, 0,1,2,3	g, 0,1,2,3	ptc, 0,1,2,3	C4d, 0,1,2,3	
BL.	, 0,1,	, 0, 2,3	v, 0,1,2,3	g, 0,1,2,3	ptc, 0,1,2,3	C4d, 0,1,2,3	
AAMR							
II.	i, 0,1,2,3	t, 0,1,2,3	v, 0,1,2,3	g, 0,	ptc, 0,	C4d, 0,1	
III.	i, 0,1,2,3	t, 0,1,2,3	v, 0,1,2,	g, 0,1,	ptc, 0,1	C4d, 0,1	DSA
ATMR							
IA.	i, 0,1,	t, 0,1, ,3	v, 0,1,2,3	g, 0,1,2,3	ptc, 0,1,2,3	C4d, 0,1,2,3	
IB.	i, 0,1,	t, 0,1,2,	v, 0,1,2,3	g, 0,1,2,3	ptc, 0,1,2,3	C4d, 0,1,2,3	
IIA.	i, 0,1,	t, 0,1	v, 0, ,2,3	g, 0,1,2,3	ptc, 0,1,2,3	C4d, 0,1,2,3	
IB.	i, 0,1,	t, 0,1	v, 0,1, ,3	g, 0,1,2,3	ptc, 0,1,2,3	C4d, 0,1,2,3	
III.	i, 0,1	t, 0,1,	v, 0,1,2	g, 0,1,2,3	ptc, 0,1,2,3	C4d, 0,1,2,3	
CAAMR							
ci, 0,	ct, 0,	cv, 0,	cg, 0,	ptcbm, 0,	mm, 0,1,2,3	ah, 0,1,2,3	
CATMR							
ci, 0,	ct, 0,	cv, 0,	cg, 0,1,2,3	ptcbm, 0,1,2,3	mm, 0,1,2,3	ah, 0,1,2,3	

History of Banff classification	
' 5 9 - ' 1 9 f f n a B	' 7 9 f f n a B
normal	normal
superacute rejection	antibody mediated rejection A: superacute rejection B: accelerated acute rejection
boaderline change	boaderline change
acute rejetcion grade I grade II A, B grade III	acute/active rejetcion type I A, B type II A, II B type III
chronic allograft nephropathy (CAN) grade I, II, III	chronic sclerosing allograft nephropathy (CSAN) grade I, II, III a or b (rejection (+))

History of Banff classification

Banff 97'	Banff 01'
normal	normal
antibody mediated rejection A: superacute rejection B: accelerated acute rejection	antibody-mediated rejection (meeting criteria of C4d + and with circulating anti-donor antibody) 1 ATN-like 2 capillary-glomerulitis, polymorphonuclear and/or mononuclear leukocytes in peritubular capillaries 3 arterial-transmural inflammation/fibrinoid change
borderline change	borderline change
acute/active rejection type I A, B type II A, II B type III	acute/active rejection type I A, B type II A, II B type III
chronic sclerosing allograft nephropathy (CSAN) grade I, II, III a or b (rejection (+))	chronic sclerosing allograft nephropathy (CSAN) grade I, II, III a or b (rejection (+))

History of Banff classification

' 1 0 f f n a B	' 5 0 f f n a B	Banff 07'
antibody-mediated rejection (meeting criteria of C4d + and with circulating anti-donor antibody)	acute antibody mediated rejection	
1 ATN-like	1 ATN-like	
2 capillary glomerulitis, polymorphonuclear and/or mononuclear leukocytes in peritubular capillaries	2 capillary glomerulitis, polymorphonuclear and/or mononuclear leukocytes in peritubular capillaries	
3 arterial-transmural inflammation/fibrinoid change	3 arterial-transmural inflammation/fibrinoid change	
borderline change	borderline change	
acute/active rejection type I A, B type II A, II B type III	T cell mediated rejection acute T cell mediated rejection type I A, B type II A, II B type III	C4d score 2003 ptc score
chronic sclerosing allograft nephropathy (CSAN) grade I, II, III a or b (rejection (+))	chronic T cell mediated rejection	
	IF/TA	

Borderline changes

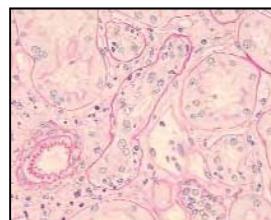
Banff 2007

'Suspicious' for acute T-cell-mediated rejection

This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis

i, 2,3 | 0, | v, 0,1,2,3 | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1,2,3

, 0,1, | , 0, 2,3 | v, 0,1,2,3 | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1,2,3



Acute antibody-mediated rejection

C4d deposition without morphologic evidence of active rejection C4d+

presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination). Cases with simultaneous borderline changes or ATN are considered as indeterminate

Banff 2007

C4d+ and DSA

morphologic evidence of acute tissue injury, such as :

- I. ATN-like minimal inflammation
- II. Capillary and/or glomerular inflammation ($\text{ptc/g} > 0$) and/or thromboses
- III. Arterial—v3

i, 0,1,2,3 | t, 0,1,2,3 | v, 0,1,2,3 | g, 0, | ptc, 0, | C4d, 0,1

i, 0,1,2,3 | t, 0,1,2,3 | v, 0,1,2, | g, 0,1, | ptc, 0,1 | C4d, 0,1

i, 0,1,2,3 | t, 0,1,2,3 | v, 0,1,2, | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1

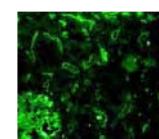


Table 1: Quantitative criteria for peritubular capillaritis¹

ptc 0	No significant cortical ptc, or <10% of PTCs with inflammation
ptc 1	≥10% of cortical peritubular capillaries with capillaritis, with max 3 to 4 luminal inflammatory cells
ptc 2	≥10% of cortical peritubular capillaries with capillaritis, with max 5 to 10 luminal inflammatory cells
ptc 3	≥10% of cortical peritubular capillaries with capillaritis, with max >10 luminal inflammatory cells

¹It is recommended that one comment on the composition (mononuclear cells vs. neutrophils) and extent (focal, ≤50% vs. diffuse, >50%) of peritubular capillaritis.



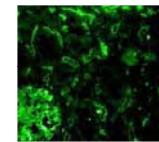
Acute antibody-mediated rejection

Banff 2007

C4d+ and DSA

morphologic evidence of acute tissue injury, such as :

- I. ATN-like minimal inflammation
- II. Capillary and or glomerular inflammation ($\text{ptc/g} > 0$) and/or thromboses
- III. Arterial—v3



Banff 2007

% biopsy area (cortex and/or medulla)	Significance and interpretation according to technique	Banff 2007	
		IF	IHC
C4d0 Negative:	0%	Neg	Neg
C4d1 Minimal	1<10%	Neg	Unknown
C4d2 Focal	10-50%	Unknown	? Pos
C4d3 Diffuse	>50%	Pos	Pos

Banff 2013

	IF	IHC
	negative	negative
	negative	positive
	positive	positive
	positive	positive



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 97 type 1A or greater) or
borderline changes

Banff 2013

Am J Transplant. 2014 Feb;14(2):272-83. doi: 10.1111/ajt.12590.

Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions.

Haas M¹, Sis B, Racusen LC, Solez K, Glotz D, Colvin RB, Castro MC, David DS, David-Neto E, Bagnasco SM, Cendales LC, Cornell LD, Demetris AJ, Drachenberg CB, Farver CF, Farris AB 3rd, Gibson IW, Kraus E, Lapiis H, Loupy A, Nickeleit V, Randhawa P, Rodriguez ER, Rush D, Smith RN, Tan CD, Wallace WD, Mengel M, as the Banff meeting report writing committee

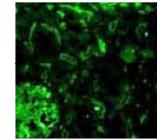
Acute antibody-mediated rejection

C4d+ and DSA

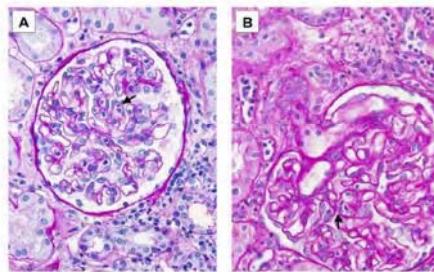
morphologic evidence of acute tissue injury, such as :

- I. ATN-like minimal inflammation
- II. Capillary and or glomerular inflammation ($\text{ptc/g} > 0$) and/or thromboses
- III. Arterial—v3

Banff 2007



**g1 = 1 loop 以上
EM でもOK**



cg0 – Banff 2013
cg no GBM double contours by LM or EM

cg1a – no GBM double contours by LM but at least three CL by EM with associated endothelial swelling and/or subendothelial electron-lucent widening

cg1b – one or more GBM double contours in 1 nonsclerotic glomerulus by LM
EM confirmation is recommended if EM is available.

Figure 1: Two examples of glomeruli with segmental glomerulitis, defined as complete or partial occlusion of ≥1 glomerular capillary by leukocyte infiltration and endothelial cell enlargement (arrows). In addition to glomerulitis, the glomerulus in panel B shows transplant glomeropathy (cg1b) with a small number of glomerular basement membrane double contours in the vicinity of the arrow, and peritubular capillitis is also present. Periodic acid-Schiff stain, original magnification $\times 400$ (both panels).

Acute/active ABMR Banff 2013

all three features must be present for diagnosis

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

Microvascular inflammation ($\text{g}>0.3$ and/or $\text{ptc}>0$)
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 ($\text{g}+\text{ptc}>2$)
Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated

3. Serologic evidence of donor-specific antibodies (DSAs)
(HLA or other antigens)

Chronic active antibody-mediated rejection

Banff 2007

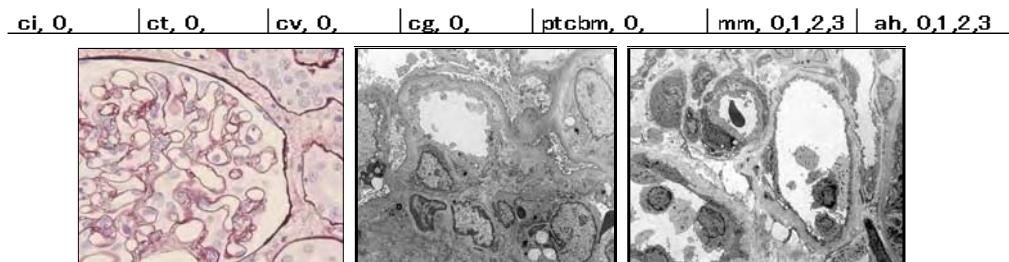
C4d+ and DSA

morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or

fibrous intimal thickening in arteries

cg1a: LM (-), EM (+) loop>0

cg1b: LM (+) loop>0



Chronic, active ABMR Banff 2013

all three features must be present for diagnosis

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
 - Transplant glomerulopathy (TG) ($cg>0$), if no evidence of chronic thrombotic microangiopathy
 - Severe peritubular capillary basement membrane multilayering (requires EM)
 - Arterial intimal fibrosis of new onset, excluding other causes
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 ($g+ptc>2$)
 - 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)

Acute T-cell-mediated rejection

Banff 2007

- IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
- IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
- IIA. Cases with mild-to-moderate intimal arteritis (v1)
- IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
- III. Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
 - IA. i, 0,1, | t, 0,1, ,3 | v, 0,1,2,3 | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1,2,3
 - IB. i, 0,1, | t, 0,1,2, | v, 0,1,2,3 | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1,2,3
 - IIA. i, 0,1, | t, 0,1 | v, 0, ,2,3 | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1,2,3
 - IB. i, 0,1, | t, 0,1 | v, 0,1, ,3 | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1,2,3
 - III. i, 0,1 | t, 0,1, | v, 0,1,2 | g, 0,1,2,3 | ptc, 0,1,2,3 | C4d, 0,1,2,3

Chronic active T-cell-mediated rejection

Banff 2007

'chronic allograft arteriopathy'
arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima

ci, 0, | ct, 0, | cv, 0 | cg, 0,1,2,3 | ptc&bm, 0,1,2,3 | mm, 0,1,2,3 | ah, 0,1,2,3 |

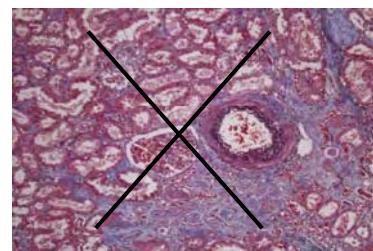
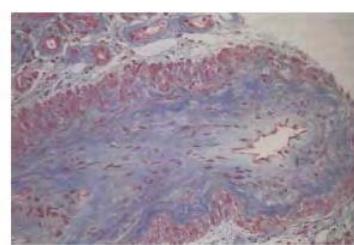
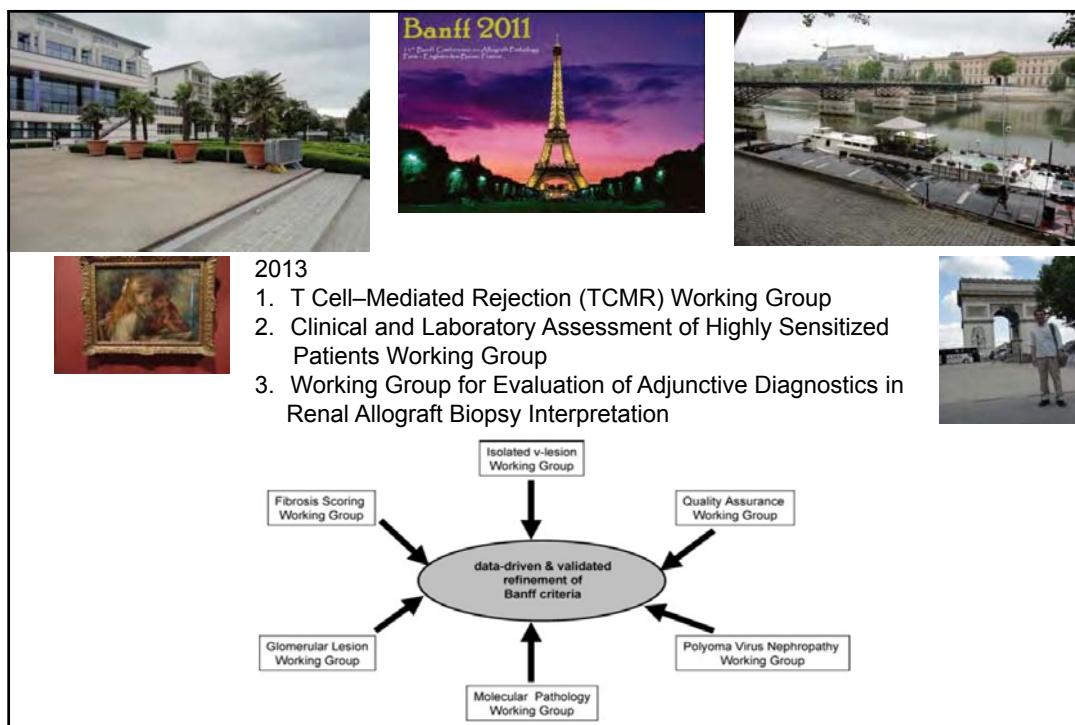


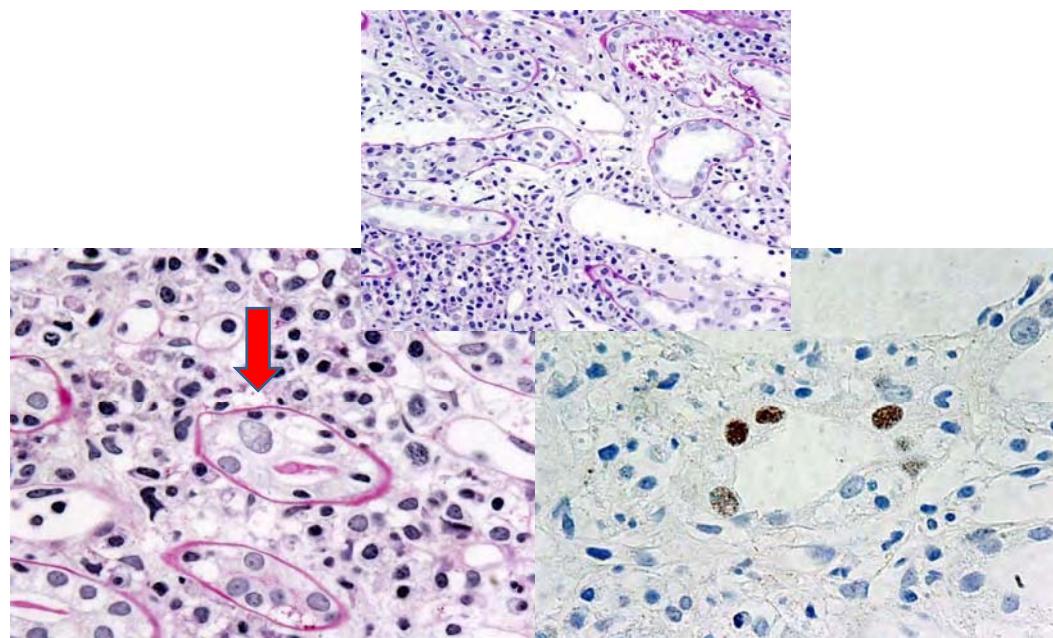
Fig. 3. Fibrous intimal thickening in a patient with chronic rejection (Masson trichrome stain, $\times 57$).

Banff 診断に基づいた病理判定

1. Banff classification history & topics
2. Banff classification WG issues
BK virus nephropathy
3. non-rejection findings
medullary ray injury (MRI)



BK virus nephropathy



Progressing report of the working group on the
classification of polyomavirus nephropathy (PVN)
2011 report

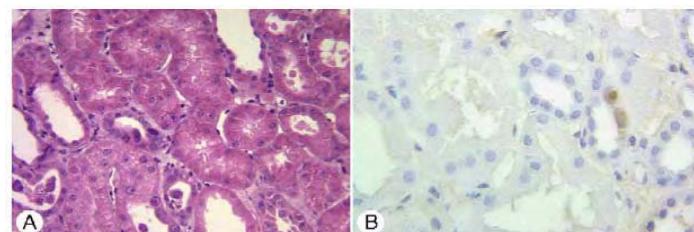
Pathological stages of PVN

Stage A medulla/cortex

Stage B medulla/cortex

Stage C medulla/cortex

Stage A



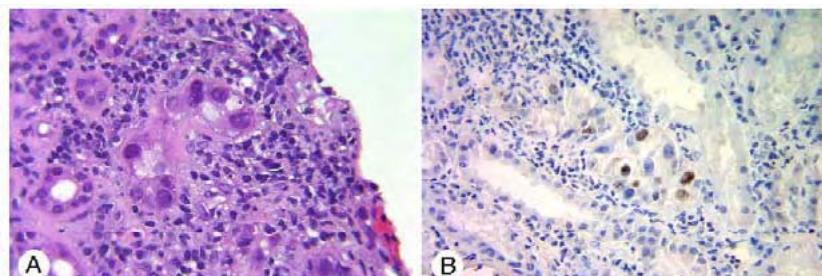
varying degree of viral replication with **intranuclear inclusion bodies** and/or positive immunohistochemistry (SV-40 T antigen) and/or in-situ hybridization signals.
No or minimal tubular epithelial cell lysis / cell necrosis
No or minimal denudation of tubular basement membrane caused by viral epithelial lysis.

Interstitial fibrosis < 50% of renal cortex (Banff chronicity score ci2)

Medulla changes limited to medulla
Cortex changes seen in cortex +/- medulla

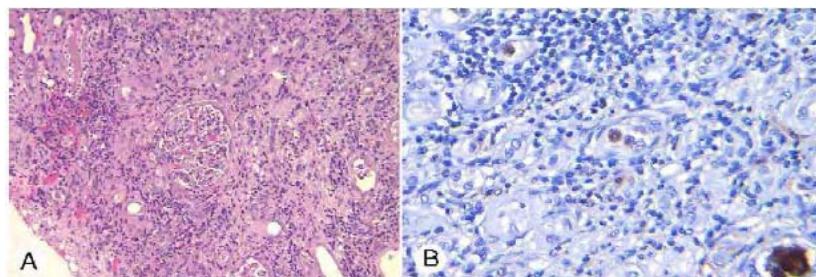
Drachenberg CB, Hum Pathol. 2005 Dec;36(12):1245-55

Stage B



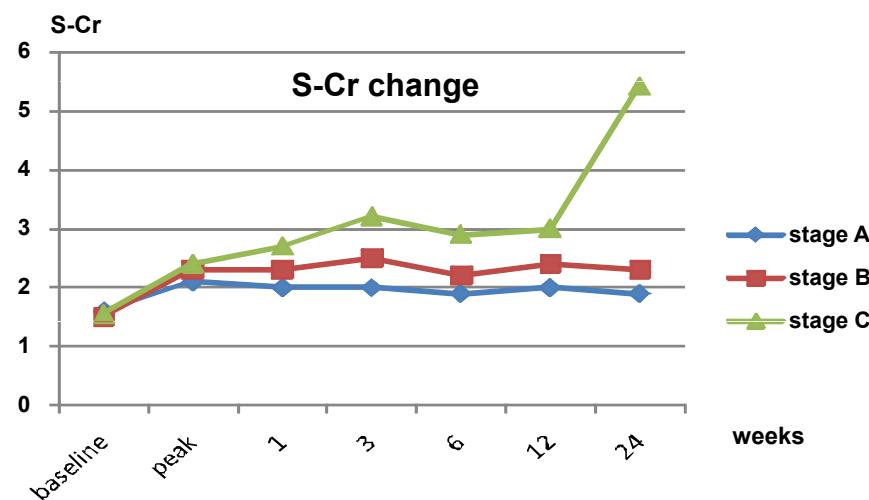
Marked virally induced tubular **epithelial cell injury/necrosis/cell lysis** with **frank denudation** of associated tubular basement membrane.

Stage C

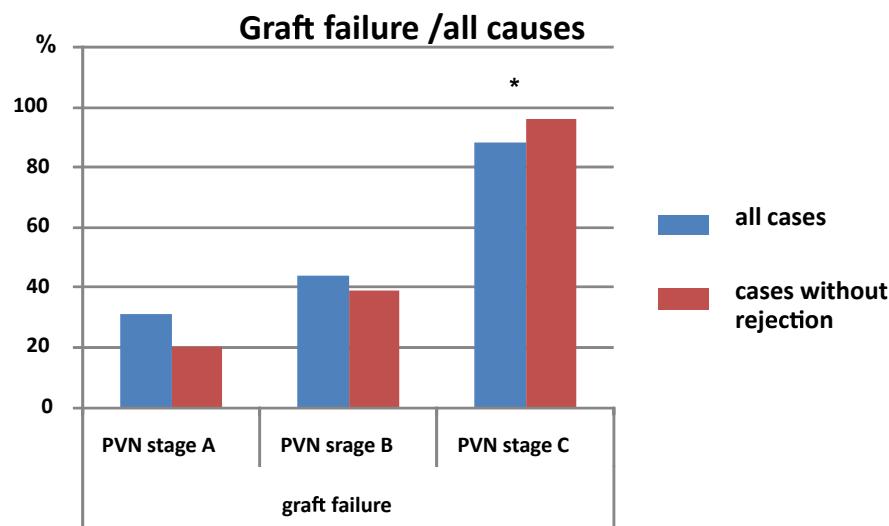


Viral replication in cortex and/or medulla (minimal to marked)
Interstitial fibrosis > 50% of cortex (Banff chronicity score=ci3)

**Progressing report of the working group on the classification of polyomavirus nephropathy (PVN)
2011 report**



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2011 report**



**Progressing report of the working group on the
classification of polyomavirus nephropathy (PVN)
2011 report**

Polyomavirus nephropathy all repeated biopsy

repeat biopsy n=22
regression 27%
stable 43%
progression 30%

**differential diagnosis between
PVN and acute rejection**

	PVN	AR
location :	medulla	cortex
C4d:	on TBM	on PTC
Infilt. cell	plasma	lymphocyte
nucleus change	(+)	(-)
SV-40	(+)	(-)

Banff 診断に基づいた病理判定

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 - BK virus nephropathy
3. non-rejection findings
 - medullary ray injury (MRI)
 - IF/TA

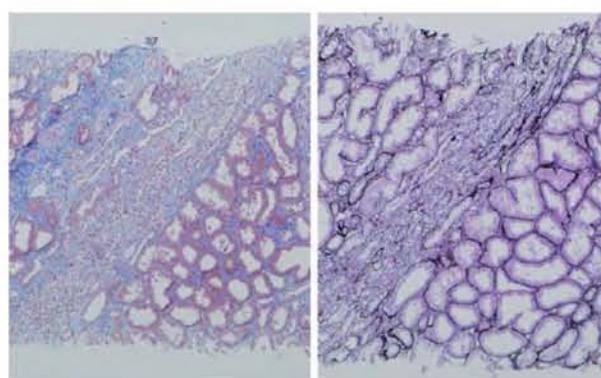
medullary ray injury (MRI)文献資料

Original Article

Medullary ray injury in renal allografts

Pathology International 2010; 60: 744–749

Akimitsu Kobayashi,¹ Izumi Yamamoto,¹ Shinichi Ito,² Yuko Akioka,³ Hiroyasu Yamamoto,¹ Satoshi Teraoka,⁴ Motoshi Hattori,² Kazunari Tanabe,⁵ Tatsuo Hosoya¹ and Yutaka Yamaguchi⁶



medullary ray injury (MRI)文献資料

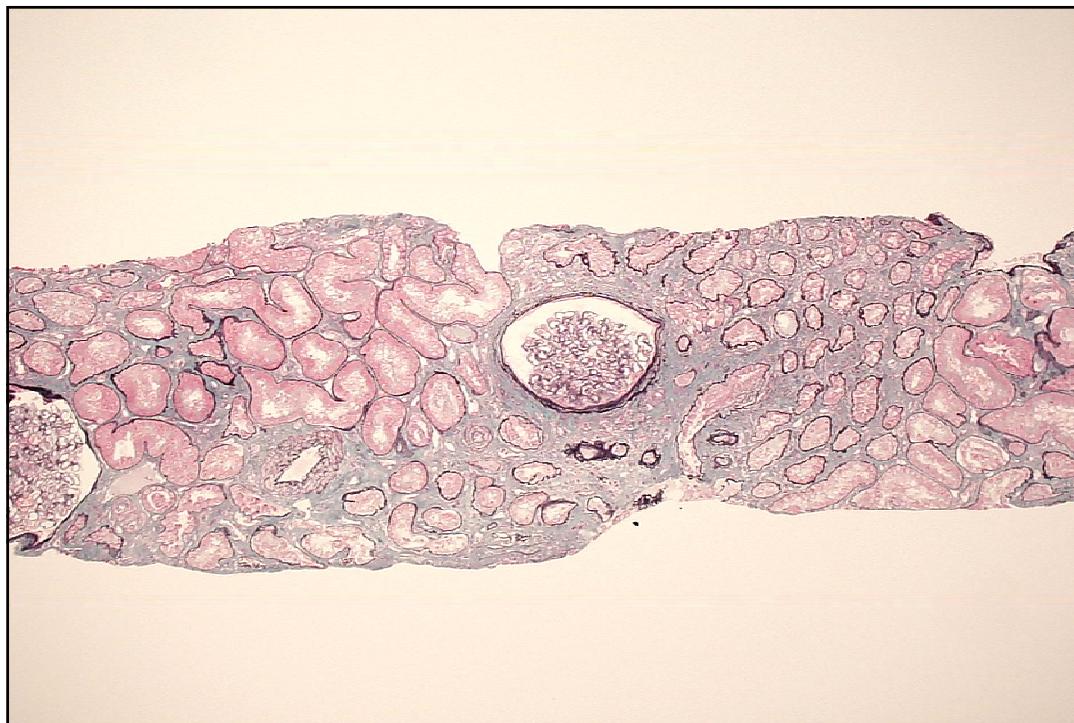
Original Article

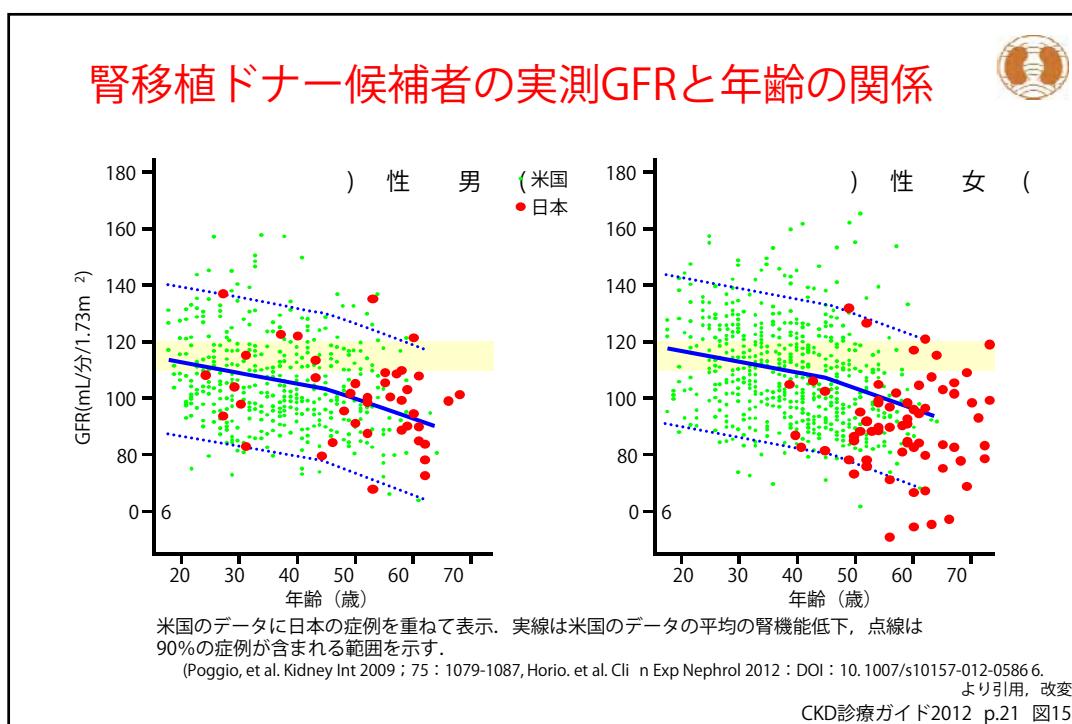
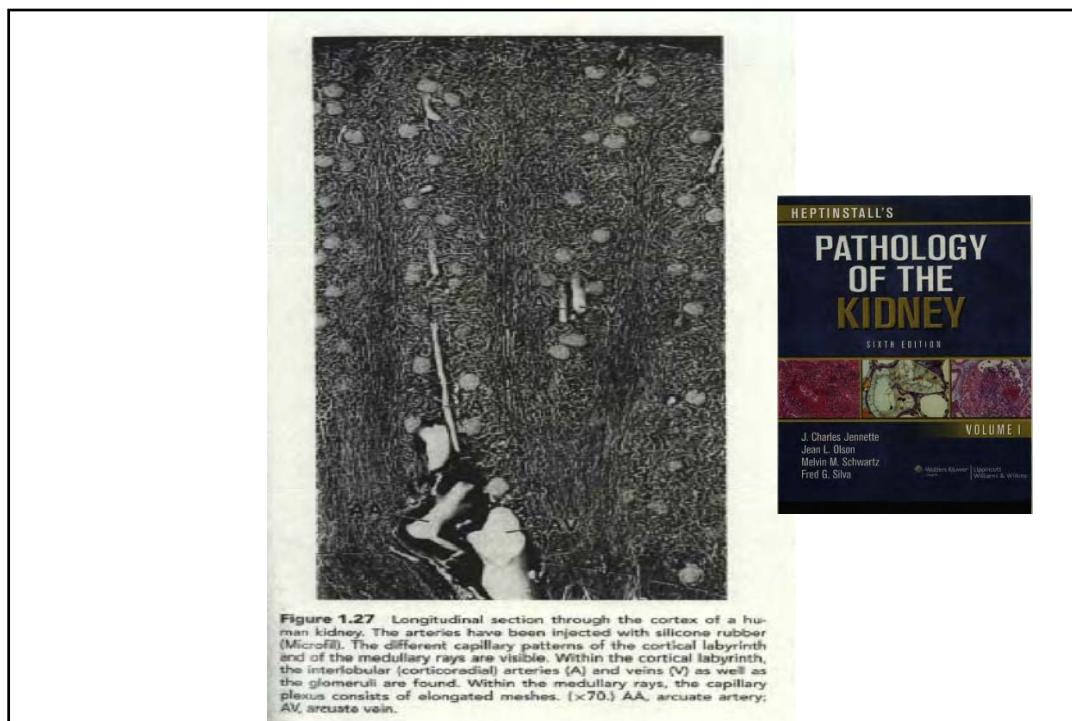
Medullary ray injury in renal allografts

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The etiology of MRI n=36
CNI toxicity (44.4%)
chronic obstruction (36.1%)
acute or chronic pyelonephritis (5.6%)
and others (13.9%)





CKDの重症度分類					
原疾患		蛋白尿区分	A1	A2	A3
糖尿病		尿アルブミン定量 (mg/日) 尿アルブミン/Cr比 (mg/gCr)	正常	微量アルブミン尿	顕性アルブミン尿
			30未満	30~299	300以上
高血圧 腎炎 多発性囊胞腎 腎移植 不明 その他		尿蛋白定量 (g/日) 尿蛋白/Cr比 (g/gCr)	正常	軽度蛋白尿	高度蛋白尿
			0.15未満	0.15~0.49	0.50以上
GFR区分 (mL/分 /1.73m ²)	G1	正常または高値	≥90	■	■
	G2	正常または軽度低下	60~89	■	■
	G3a	軽度~中等度低下	45~59	■	■
	G3b	中等度~高度低下	30~44	■	■
	G4	高度低下	15~29	■	■
	G5	末期腎不全 (ESKD)	<15	■	■

重症度は原疾患・GFR区分・蛋白尿区分を合わせたステージで評価する。CKDの重症度は死亡、末期腎不全、心血管死亡発症のリスクのステージを基準に、■、オレンジ■、赤■の順にステージが上昇するほどリスクは上昇する。

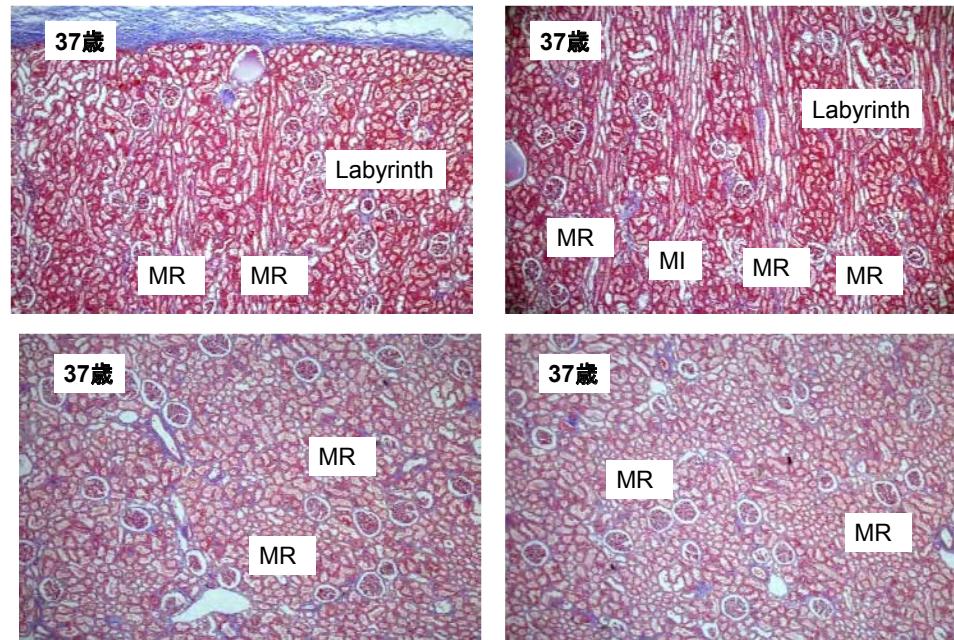
(KDIGO CKD guideline 2012を日本人用に改変)
CKD診療ガイド2012 p.3 表2

日本におけるCKD患者数(%) (20歳以上)			
GFR ステージ	GFR (mL/分/1.73m ²)	尿蛋白 -~±	尿蛋白 1+以上
G1	≥90	2,803万人	61万人(0.6%)
G2	60~89	6,187万人	171万人(1.7%)
G3a	45~59	886万人(8.6%)	58万人(0.6%)
G3b	30~44	106万人(1.0%)	24万人(0.2%)
G4	15~29	10万人(0.1%)	9万人(0.1%)
G5	<15	1万人(0.01%)	4万人(0.03%)

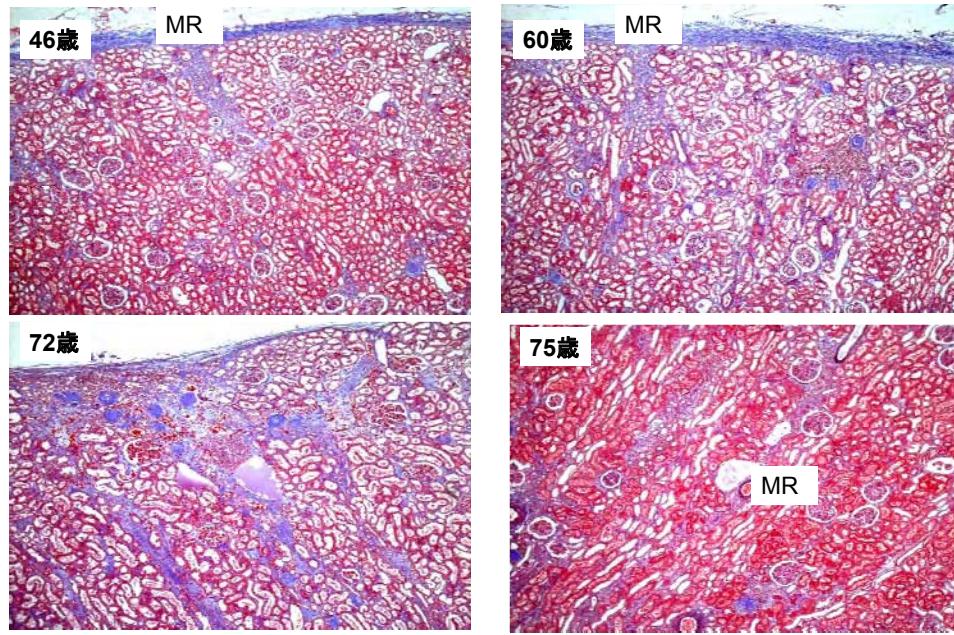
のところが、CKDに相当する

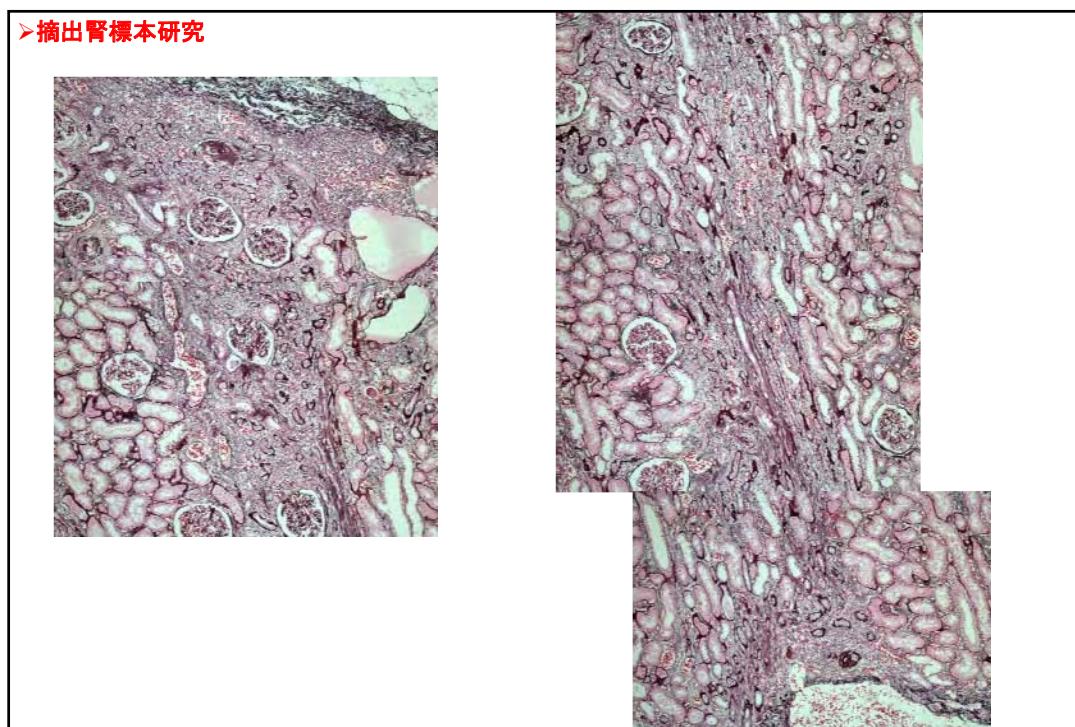
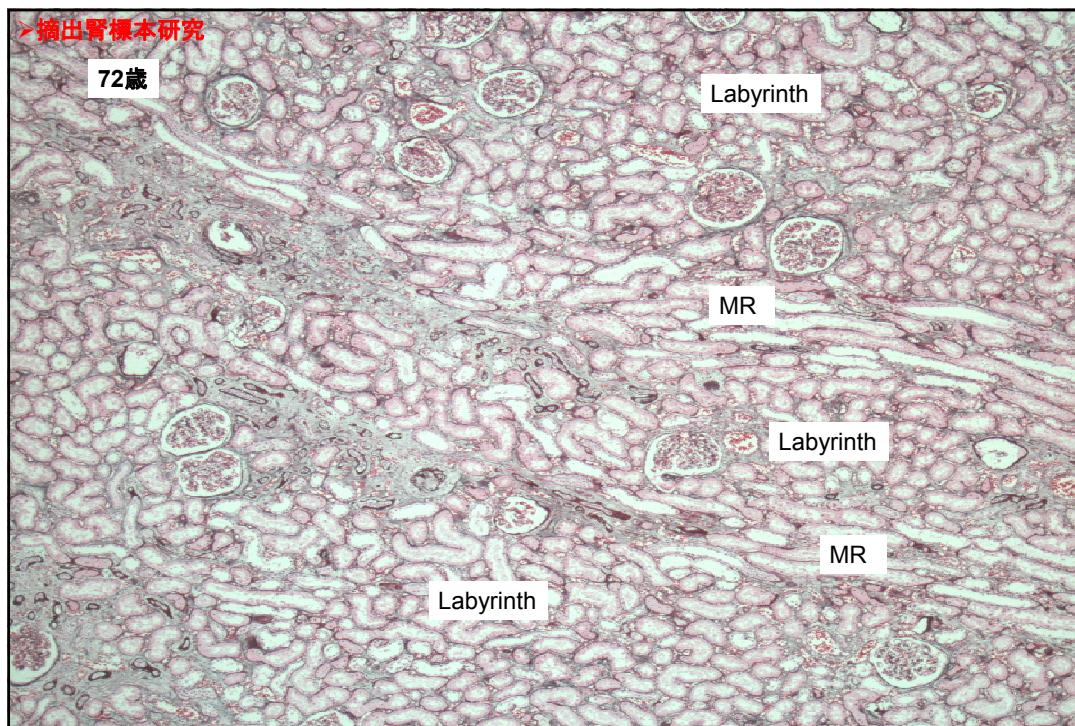
(平成23年度厚生労働省CKDの早期発見・予防・治療標準化・進展阻止に関する研究班
CKD診療ガイド2012 p.6 表4)

➤摘出腎標本研究

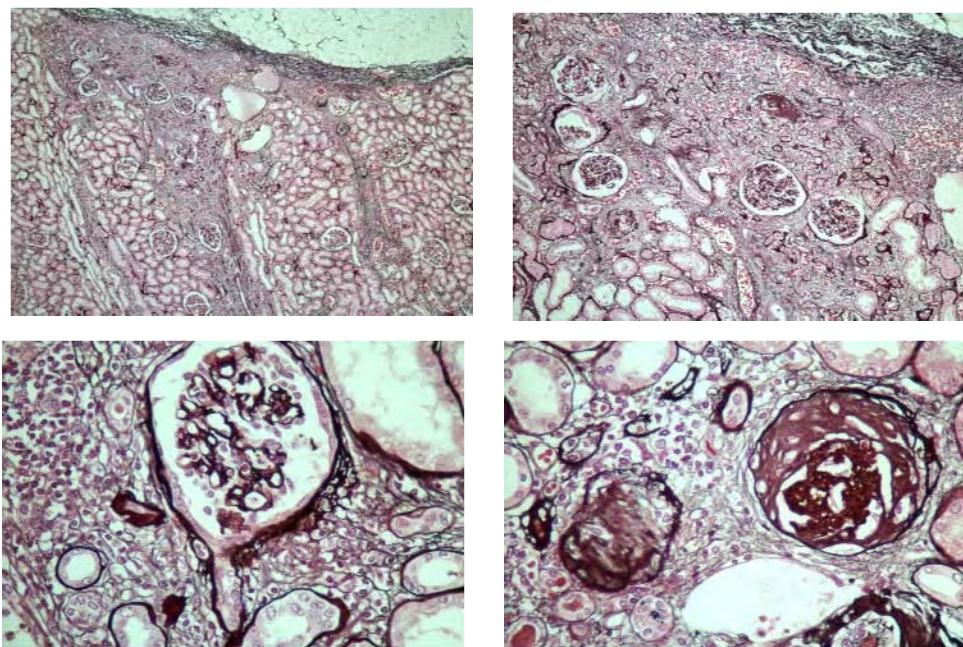


➤摘出腎標本研究





▶摘出腎標本研究



medullary ray injury (MRI)文献資料

Original Article

Medullary ray injury in renal allografts

Pathology International 2010; **60**: 744–749

Akimitsu Kobayashi,¹ Izumi Yamamoto,¹ Shinichi Ito,² Yuko Akioka,³ Hiroyasu Yamamoto,¹ Satoshi Teraoka,⁴ Motoshi Hattori,³ Kazunari Tanabe,⁵ Tatsuo Hosoya¹ and Yutaka Yamaguchi⁶

The etiology of MRI n=36
CNI toxicity (44.4%)
chronic obstruction (36.1%)
acute or chronic pyelonephritis (5.6%)
and others (13.9%)

aging and ischemic damages

Banff 診断に基づいた病理判定

1. Banff classification history & topics
2. Banff classification WG issues
 - BK virus nephropathy
3. non-rejection findings
 - medullary ray injury (MRI)
 - IF/TA

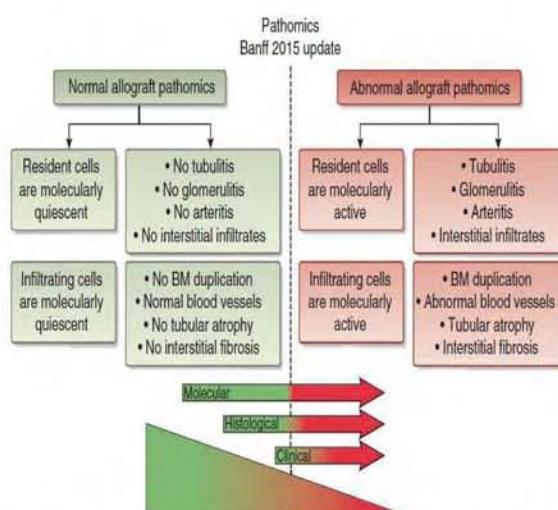


Figure 4 | Presentation slide by Thangamani Muthukumar in the style of Wired Magazine's FOUND: Artifacts from the Future speculating on what the state of science will be at the Banff 2015 meeting. 'Pathomics' is a term from a 2007 editorial by Robert Colvin.³⁶ BM, basement membrane.

The Banff classification revisited
Kidney International 2012. Kidney Int. 2013 Feb;83(2):201-6. Epub 2012 Dec 12.
Solez K, and Racusen LC

日本臨床腎移植学会 2014
COI 開示
筆頭発表者名:西 慎一

**演題発表に関し、開示すべきCOI関係にある企業
はありません。**