HIGHLIGHTS IN EMATOLOGIA
Treviso, Ospedale Ca' Foncello
22-23 Novembre 2019

Gammopatie monoclonali di significato renale (MGRS)

IKMG
International Kidney & Monoclonal Gammopathy Research Group

Mauro Dugo
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AULSS 2 –Veneto-Treviso

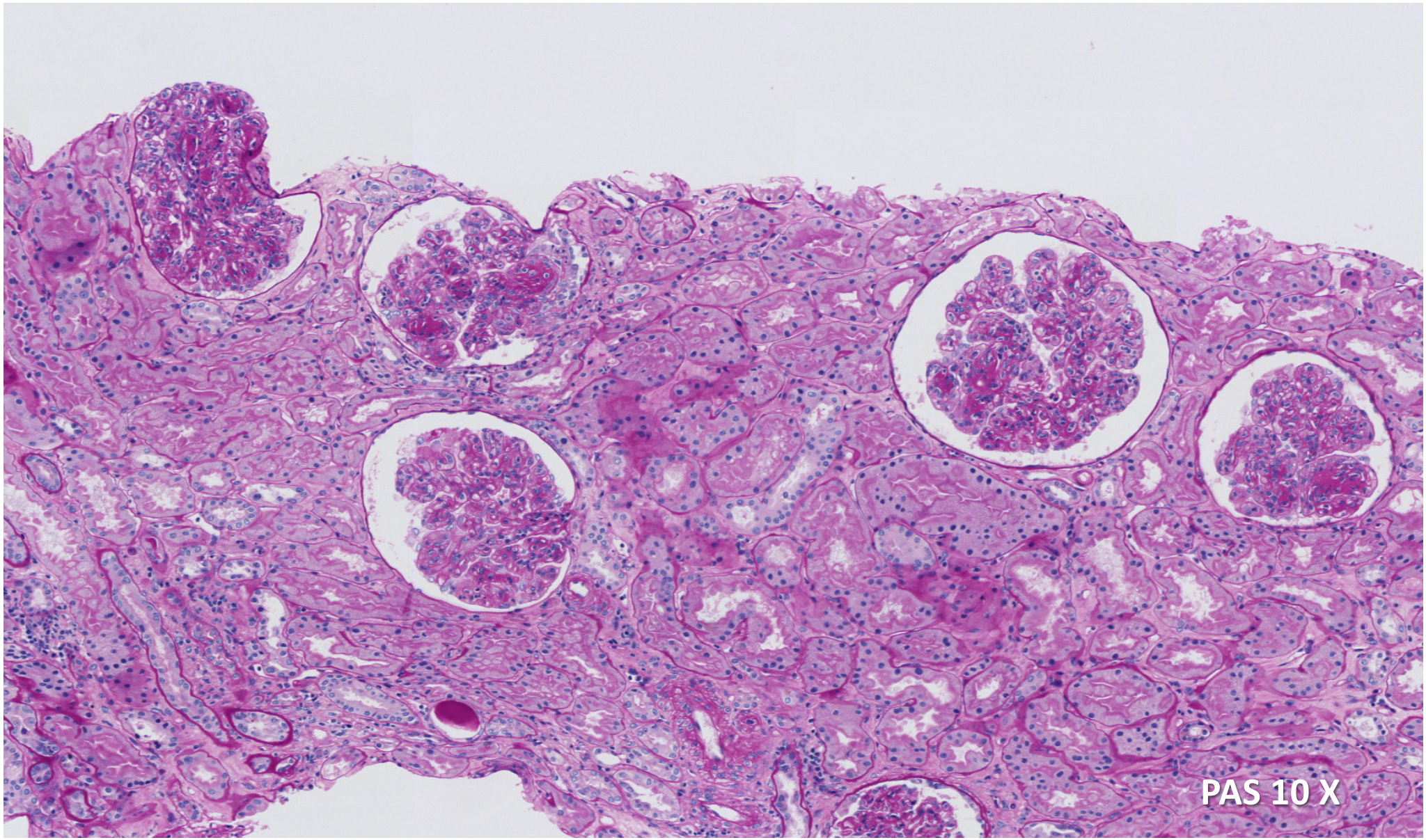
Caso clinico

Donna di 76 anni. Non allergie, isterectomia per fibromatosi. Protesi ginocchio sinistro. Cardiopatia ipertensiva.

20.7.19 ricovero in ambiente chirurgico per colecistite alitiasica, pancreatite (TC). ColangioRMN: IPMN. Colecisti con pareti edematose. Terapia antibiotica. Per febbre persistente, non chirurgica, il 28.8.19 trasferimento in MI a Treviso. Esami microbiologici negativi. Prove immunologiche : **C4 2 mg/dl, C3 82 mg/dl, criocrito 3% IgG policlonale e IgM K monoclonale (2° tipo sec Brouet), RT 46 U/mL , Elettroforesi sierica componente M IgM K (0.2 g/dl). BJ negativa. IgG4 nella norma. ANA 1:160 punteggiato, Ac SSA 236 UA/mL.** NT-PROBNP 1814 pg/ml (0-125).

Contrazione della diuresi e comparsa di porpora agli arti inferiori. Per comparsa di AKI (**Creat 1.5 mg/dl, max 2.7 mg/dl**), es urine: **prot 300 mg/dl, 150 GR/campo, cilindri jalini** veniva trasferita in Nefrologia. Proteinuria frazionata di tipo glomerulare non selettivo.

6.9.19 BIOPSIA RENALE SINISTRA IN POSIZIONE LATERALE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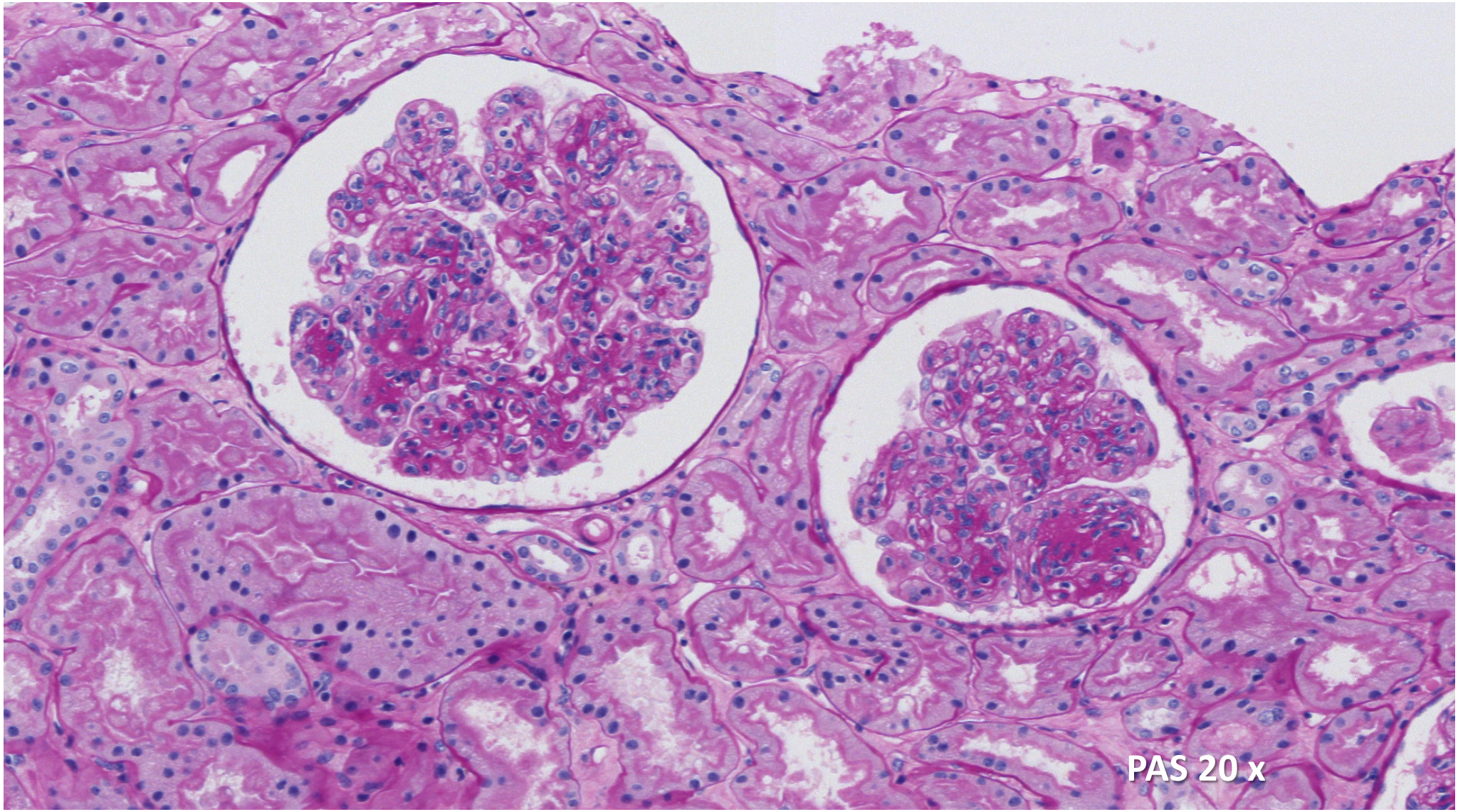
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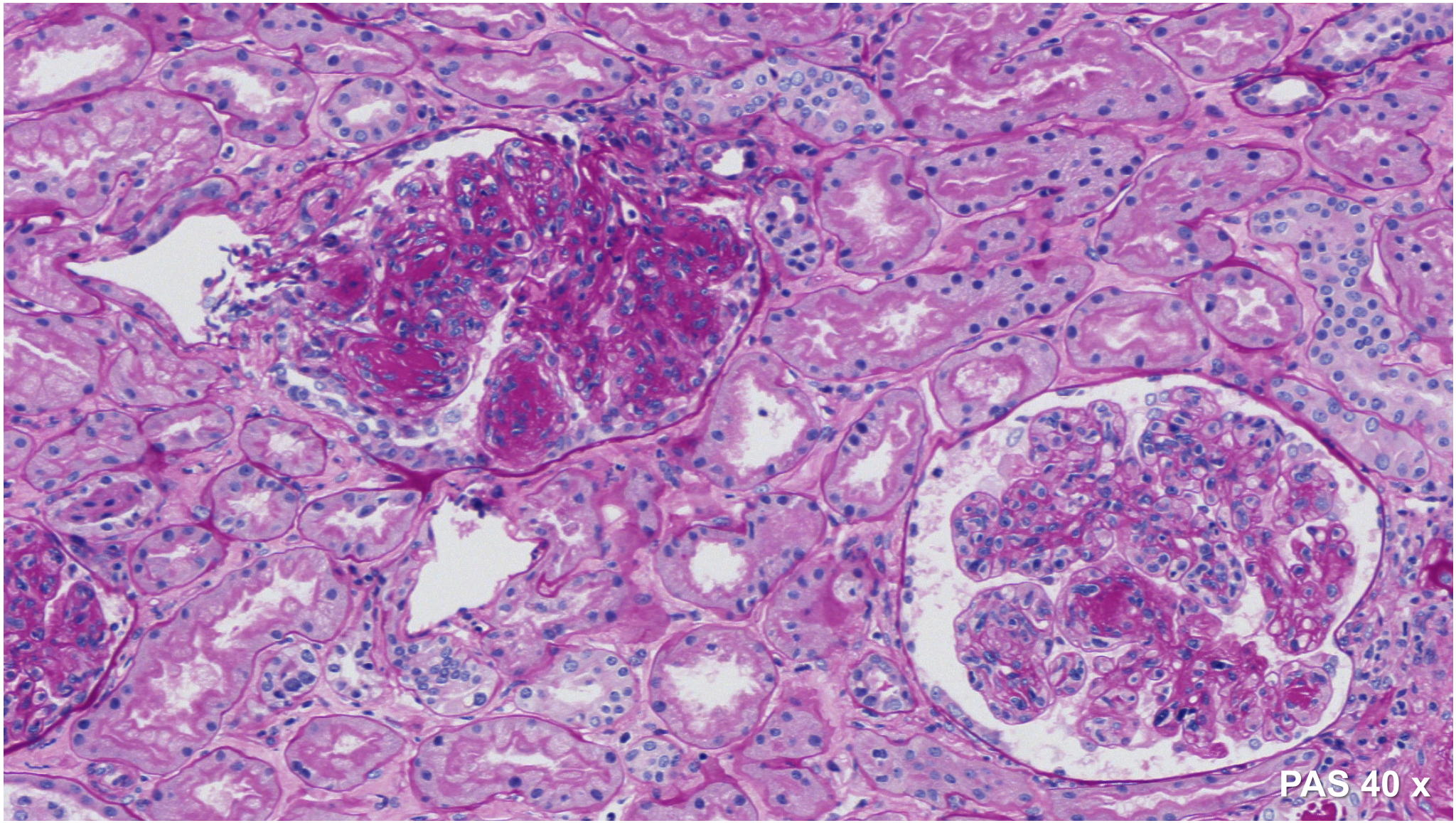
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Referto MO-IF

MO

Frustolo comprendente fino a 40 glomeruli, 2 jalini, caratterizzati da profilo lobulato e proliferazione diffusa endocapillare con presenza di monociti e granulociti neutrofili. In alcuni glomeruli si reperta materiale jalino endocapillare. Infiltrati infiammatori sparsi interstiziali linfomonocitari, atrofia tubulare focale. Ialinosi arteriolare, non aspetti di vasculite.

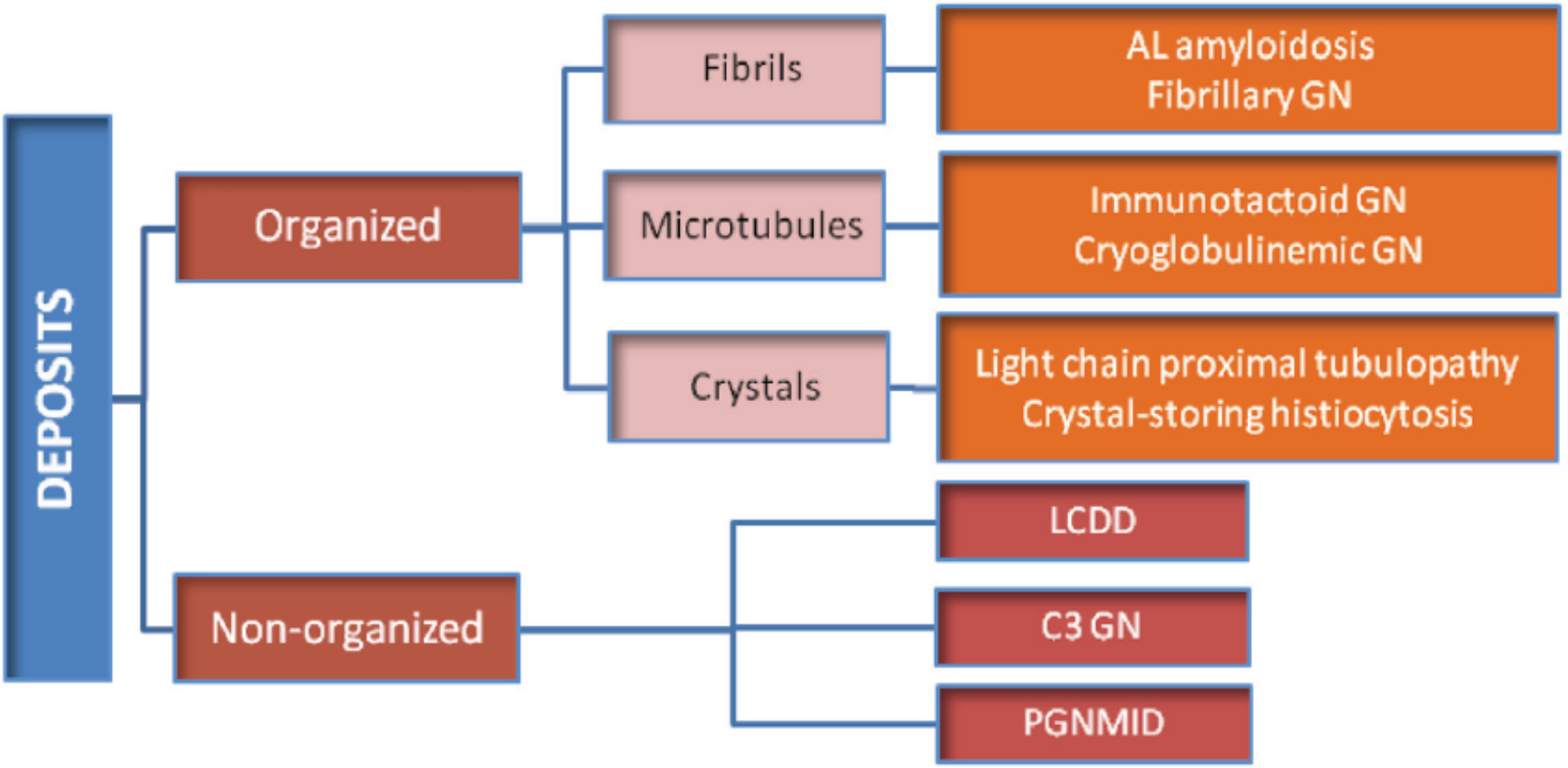
IF

positività diffusa di C3, meno intensa per IgM e K.

Conclusioni: quadro istologico di GNMP .

Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

Nelson Leung,[1,2] Frank Bridoux,[3] Colin A. Hutchison,[4] Samih H. Nasr,[5] Paul Cockwell,[4] Jean-Paul Fermand,[6] Angela Dispenzieri,[2] Kevin W. Song,[7] and Robert A. Kyle,[2] on behalf of the International Kidney and Monoclonal Gammopathy Research Group



Pathophysiology and management of monoclonal gammopathy of renal significance

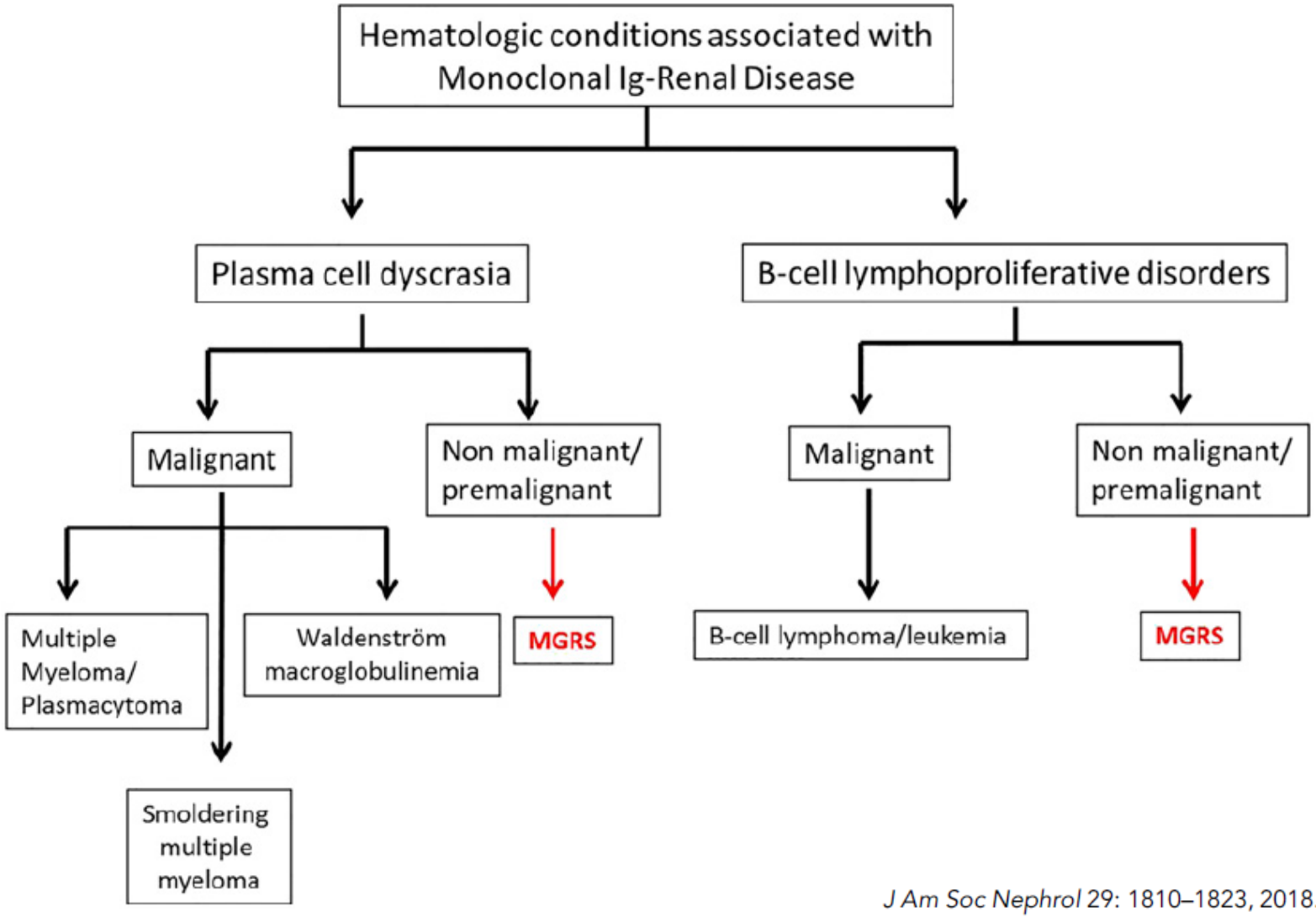
Ankur Jain,[1] Richard Haynes,[2,3] Jaimal Kothari,[4,5] Akhil Khera,[4] Maria Soares,[6] and Karthik Ramasamy[4,5,7]

Epidemiology and clinical importance of MGRS

MGRS has been estimated from previous observations at 10% of cases of MGUS, with a prevalence of 0.32% and 0.53% in people older than 50 years and 70 years, respectively.[5,13] Since its first formal description in 2012, published evidence describe the natural history of MGRS. Key findings from these studies are listed below.

The Complexity and Heterogeneity of Monoclonal Immunoglobulin–Associated Renal Diseases

Sanjeev Sethi,[1] S. Vincent Rajkumar,[2] and Vivette D. D'Agati[3]



J Am Soc Nephrol 29: 1810–1823, 2018.

The Complexity and Heterogeneity of Monoclonal Immunoglobulin–Associated Renal Diseases

Table 1. Criteria for monoclonal gammopathy of underdetermined significance, monoclonal gammopathy of renal significance, smoldering multiple myeloma, and multiple myeloma

MGUS	MGRS	Smoldering Multiple Myeloma	Multiple Myeloma
<10% Clonal BMPCs and	<10% Clonal BMPCs and	10%–60% Clonal BMPCs or	Clonal plasma cell disorder (≥10% clonal BMPCs or biopsy-proven plasmacytoma) and one or more of following MDEs: ≥60% BMPCs, ≥100 FLC ratio, more than one MRI focal lesion, or CRAB features (see below)
<3 g/dl M protein	<3 g/dl M protein[a] and	≥3 g/dl Serum M protein or ≥500 mg/24 h urinary M protein	M protein in serum and/or urine present in all patients except true nonsecretory myeloma
No end organ damage	Monoclonal Ig–associated renal disease[b]	No end organ damage[b]	CRAB features[b] attributable to plasma cell disorder
No MDE	No MDE	No MDE	MDE present

MGUS, monoclonal gammopathy of underdetermined significance; MGRS, monoclonal gammopathy of renal significance; BMPC, bone marrow plasma cell; MDE, myeloma-defining event; FLC, free light chain' MRI, magnetic resonance imaging; CRAB, hypercalcemia, renal insufficiency, anemia, bone lesions; M protein, monoclonal protein.

[a]In small percentage of MGRS, there is a monoclonal Ig–associated renal disease but no detectable M protein, and in a small percentage of MGRS, there may be no detectable M protein but an abnormal FLC ratio.

[b]Any of the renal disorders included under the term MGRS can occur in patients with smoldering multiple myeloma or multiple myeloma.

J Am Soc Nephrol 29: 1810–1823, 2018.

Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

Nelson Leung,[1,2] Frank Bridoux,[3] Colin A. Hutchison,[4] Samih H. Nasr,[5] Paul Cockwell,[4] Jean-Paul Fermand,[6] Angela Dispenzieri,[2] Kevin W. Song,[7] and Robert A. Kyle,[2] on behalf of the International Kidney and Monoclonal Gammopathy Research Group

In conclusion, MGRS-related kidney diseases are the result of toxic monoclonal protein produced by dangerous, small B-cell clones.[12] These disorders do not require treatment from a "tumoral" viewpoint (ie, their bulk and proliferative rate), but treatment is often mandatory and sometimes urgent to prevent renal deterioration. In the past, there was a reluctance to use chemotherapy in patients without myeloma or AL amyloidosis. Therapies with novel agents have lessened the risk of treatment. Recovery of renal function is possible with adequate hematologic response. Even in patients with ESRD, treatment may be appropriate if kidney transplantation is being considered. The time has come for a term that separates MM and MGUS from monoclonal gammopathies that result in renal damage. We think the term "monoclonal gammopathy of renal significance" fulfills this role. The term MGUS should be limited to those cases where no connection to end organ damage can be demonstrated. Meanwhile, MGRS should be used when the monoclonal protein is playing a direct role in the kidney disease. This distinction will hopefully alert the physician to the seriousness of these conditions and clarify the role of chemotherapy.

Review in translational hematology

Dangerous small B-cell clones

Giampaolo Merlini and Marvin J. Stone

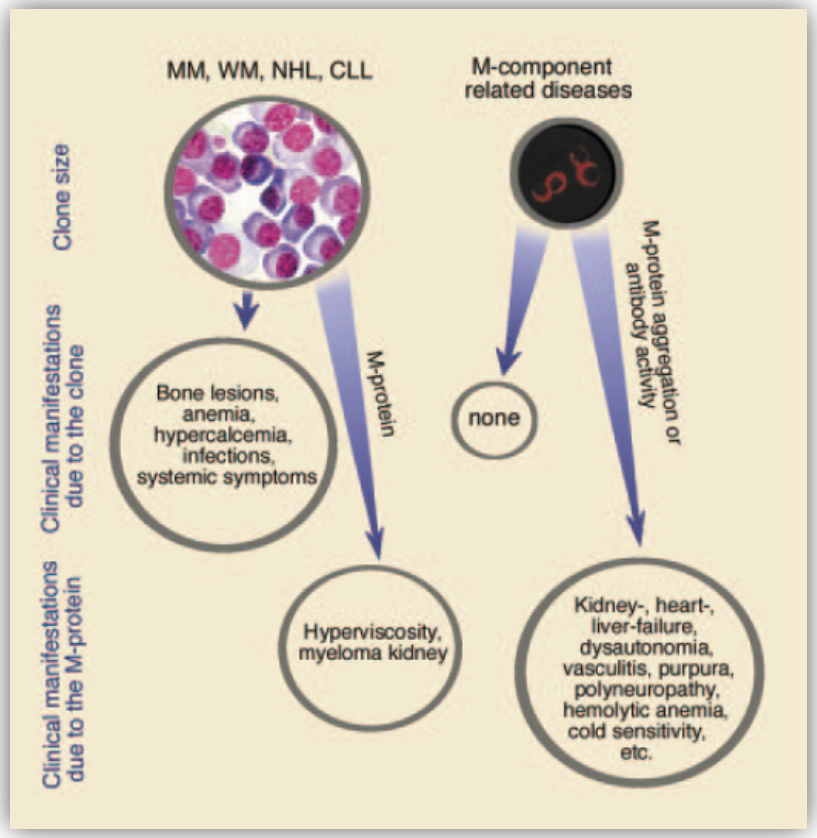


Table 1. Most common monoclonal component-related diseases

Diseases caused by M-protein aggregation
Light chain-cast nephropathy
AL amyloidosis
Light chain-deposition disease
Crystal-storing histiocytosis: adult Fanconi syndrome
Cryoglobulinemia type I
Diseases caused by M-protein antibody activity
Mixed cryoglobulinemia type II
Monoclonal cold agglutinins
Polyneuropathies

Bridging the Divide: An Onco-Nephrologic Approach to the Monoclonal Gammopathies of Renal Significance

The Diagnostic Approach to MGRS

It is imperative to recognize that the absolute number of clonal cells may not correlate with disease burden from the MIg. In their classic review, Merlini and Stone (16) describe the MIg-mediated disorders as arising from "dangerous small B-cell clones." For context, a normal bone marrow may have up to 3% polyclonal plasma cells. Patients with MGUS have <10% clonal plasma cells. Patients with smoldering MM may have 10%–59% clonal plasma cells. The updated criteria for active MM requiring therapy includes patients with ≥60% clonal plasma cells. However, the critical distinction between MGUS/smoldering MM and MGRS is not the quantity of the plasma cell clone and its secreted paraprotein, but whether it results in end organ damage. Amyloid light-chain (AL) amyloidosis is an instructive example: a disease associated with significant end organ damage, morbidity, and mortality, yet the majority of patients have bone marrow biopsies exhibiting <10% plasma cells (17). The diagnostic approach in MGRS should similarly be sensitive enough to detect "small" plasma cell and B cell clones that do not meet criteria for overt lymphoma or MM. Extrarenal symptoms

Clin J Am Soc Nephrol 11: 1681–1691, 2016

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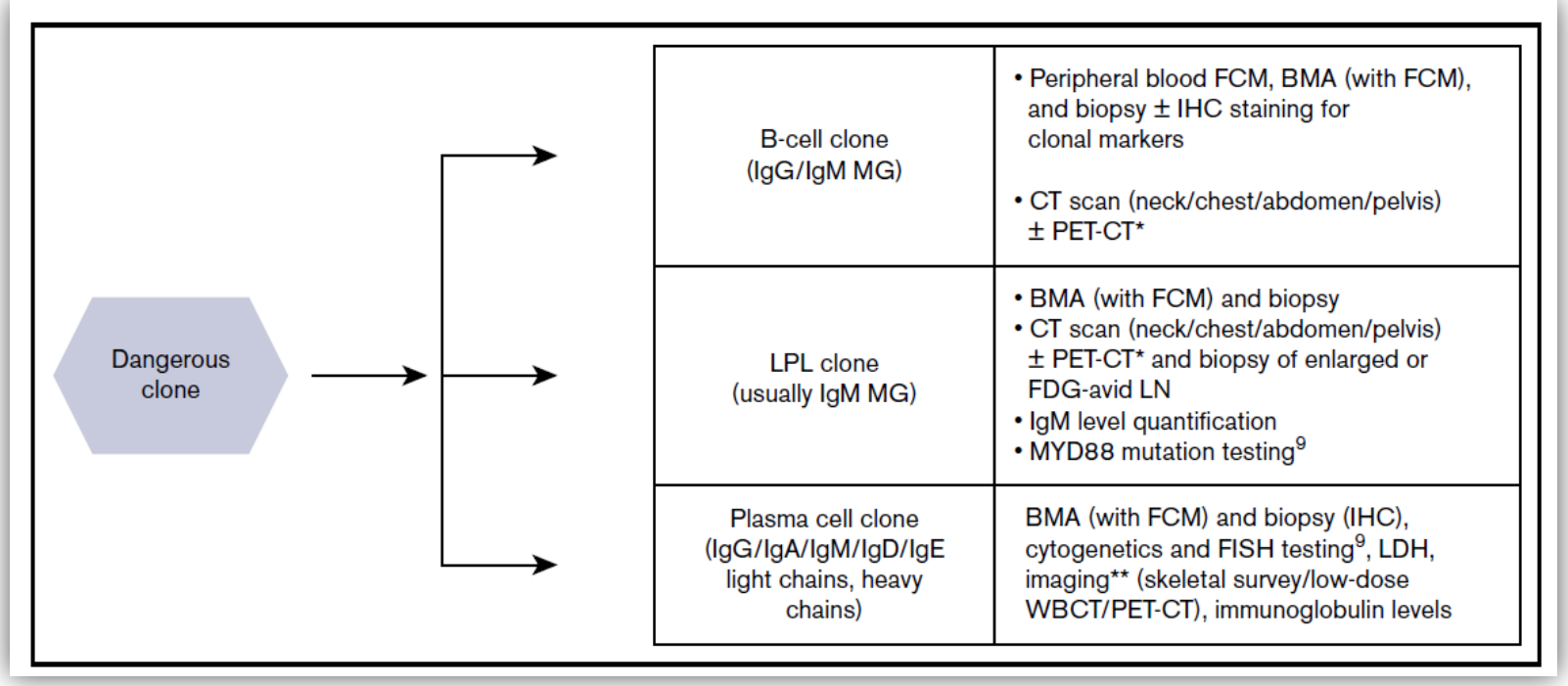
MG refers to the presence of monoclonal immunoglobulin in the serum/urine in its intact form or as fragments produced by an expanded clone of B cells, plasma cells, or lymphoplasmacytic cells. Whereas plasma cells secrete a range of monoclonal proteins, intact immunoglobulin (immunoglobulin G [IgG] > IgA > IgM > IgD > IgE), and free light chains, B cells and lymphoplasmacytic cells typically produce IgM > IgG.[3,4]



B-cell clone (IgG/IgM MG)	• Peripheral blood FCM, BMA (with FCM), and biopsy ± IHC staining for clonal markers • CT scan (neck/chest/abdomen/pelvis) ± PET-CT*
LPL clone (usually IgM MG)	• BMA (with FCM) and biopsy • CT scan (neck/chest/abdomen/pelvis) ± PET-CT* and biopsy of enlarged or FDG-avid LN • IgM level quantification • MYD88 mutation testing[9]
Plasma cell clone (IgG/IgA/IgM/IgD/IgE light chains, heavy chains)	BMA (with FCM) and biopsy (IHC), cytogenetics and FISH testing[9], LDH, imaging** (skeletal survey/low-dose WBCT/PET-CT), immunoglobulin levels

Bridging the Divide: An Onco-Nephrologic Approach to the Monoclonal Gammopathies of Renal Significance

Jonathan J. Hogan and Brendan M. Weiss†*

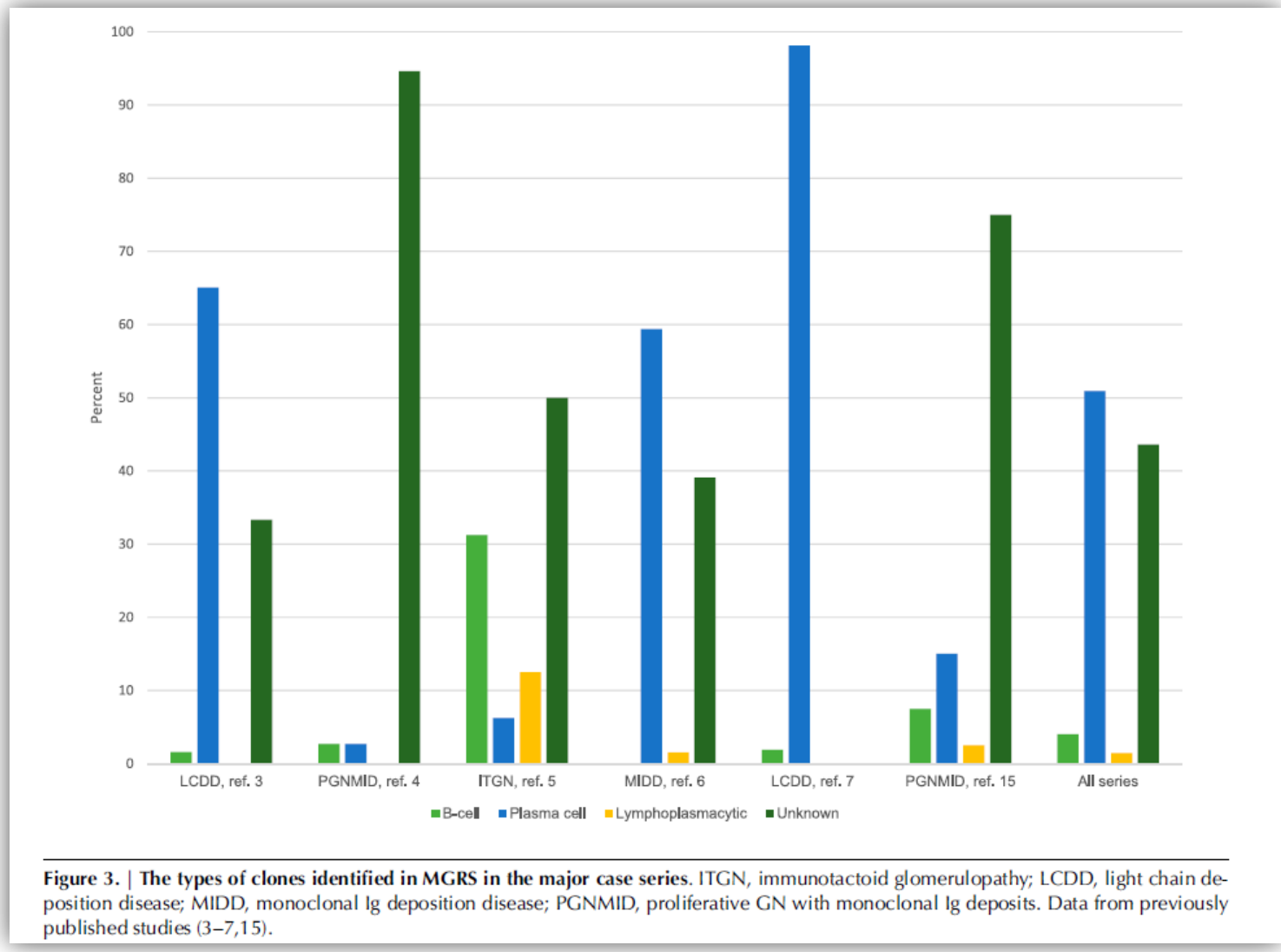


Figure 3. | The types of clones identified in MGRS in the major case series. ITGN, immunotactoid glomerulopathy; LCDD, light chain deposition disease; MIDD, monoclonal Ig deposition disease; PGNMID, proliferative GN with monoclonal Ig deposits. Data from previously published studies (3–7,15).

Clin J Am Soc Nephrol 11: 1681–1691, 2016

Bridging the Divide: An Onco-Nephrologic Approach to the Monoclonal Gammopathies of Renal Significance

Jonathan J. Hogan and Brendan M. Weiss†*

Table 1. Kidney outcomes in the largest monoclonal gammopathies of renal significance case series

MGRS Disorder	*N*	Average Follow-Up (mo)	Kidney Outcomes
LCDD (3)	63	28	57% ESRD
PGNMID (4)	37	30	38% complete/partial recovery 38% persistent renal dysfunction 22% ESRD
ITGN (5)	16	48	50% remission 33% persistent renal dysfunction 17% ESRD
MIDD (6)	64	25	39% ESRD 57% stable/improved renal function
LCDD (7)	53	74	53% ESRD (10% ESRD at presentation)

MGRS, monoclonal gammopathies of renal significance; LCDD, light chain deposition disease; PGNMID, proliferative GN with monoclonal Ig deposits; ITGN, immunotactoid glomerulopathy; MIDD, monoclonal Ig deposition disease.

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There is an urgent need to maintain awareness of MGRS in routine hematology, pathology, and nephrology practice, working in a multidisciplinary setting, to prevent end-stage renal damage and surveillance to monitor for progression to an overt hematological malignancy.

EXPERT CONSENSUS DOCUMENT

The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group

Nelson Leung[1], Frank Bridoux[2], Vecihi Batuman[3], Aristeidis Chaidos[4], Paul Cockwell[5], Vivette D. D'Agati[6], Angela Dispenzieri[1], Fernando C. Fervenza[1], Jean-Paul Fermand[7], Simon Gibbs[8], Julian D. Gillmore[9], Guillermo A. Herrera[10], Arnaud Jaccard[11], Dragan Jevremovic[1], Efstathios Kastritis[12], Vishal Kukreti[13], Robert A. Kyle[1], Helen J. Lachmann[9], Christopher P. Larsen[14], Heinz Ludwig[15], Glen S. Markowitz[6], Giampaolo Merlini[16], Peter Mollee[17], Maria M. Picken[18], Vincent S. Rajkumar[1], Virginie Royal[19], Paul W. Sanders[20], Sanjeev Sethi[1], Christopher P. Venner[21], Peter M. Voorhees[22], Ashutosh D. Wechalekar[9], Brendan M. Weiss[23] and Samih H. Nasr[1]*

Box 1 | **Updated definition of MGRS**

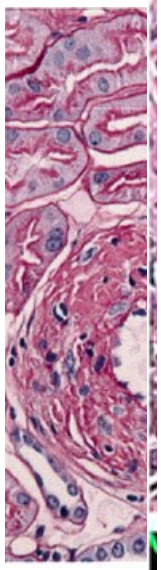
The following consensus view of monoclonal gammopathy of renal significance (MGRS) has emerged.

The term MGRS applies specifically to any B cell or plasma cell clonal lymphoproliferation with both of the following characteristics:

- One or more kidney lesions that are related to the produced monoclonal immunoglobulin
- The underlying B cell or plasma cell clone does not cause tumour complications or meet any current haematological criteria for specific therapy

Once the haematological condition progresses to overt MM, WM, advanced stage CLL or malignant lymphoma (as defined by their respective established disease criteria), these diseases are no longer considered MGRS and affected patients are managed according to disease-specific protocols.

plasmic AL amyloidosis occurs rarely[45]. The randomly arranged fibrils seen in fibrillary glomerulonephritis are on average twice as thick (10–30 nm) as those observed in amyloidosis (FIG. 3b) and generally do not stain with Congo red[44]. A small subgroup (7–17%) of patients with fibrillary glomerulonephritis demonstrates clinical evidence of a monoclonal gammopathy. In 3–15% of these patients, the IgG deposits exhibit light-chain restriction[44,46,47], and this pathology is termed monoclonal fibrillary glomerulonephritis. Glomerular staining for DnaJ homologue subfamily B member 9 (DNAJB9) is a reliable marker for fibrillary glomerulonephritis[48]. This feature can be used to distinguish monoclonal fibrillary glomerulonephritis from AHL and AH amyloidosis, especially as fibrillary glomerulonephritis can sometimes show Congo red staining[49,50].



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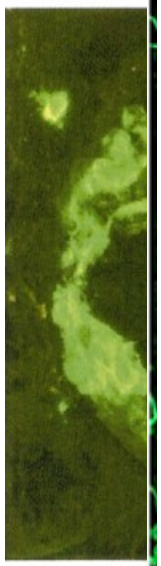


D.

Review Article

Cardiac amyloidosis: A comprehensive review ☆

Michal Fikrle[a]

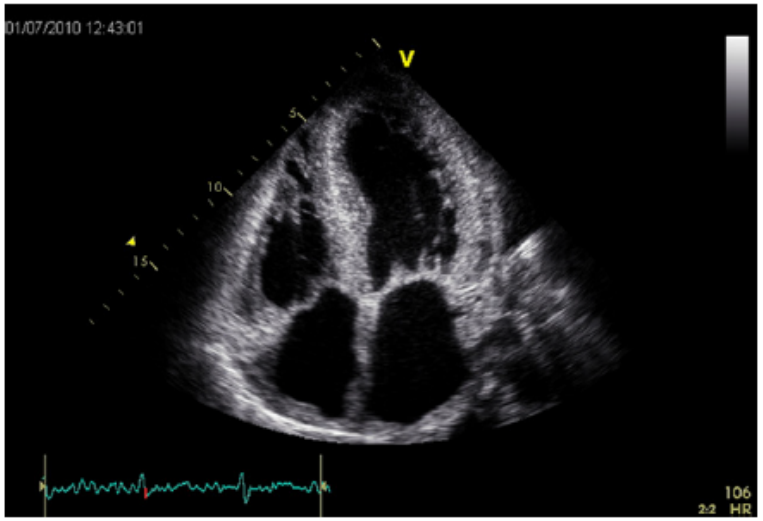
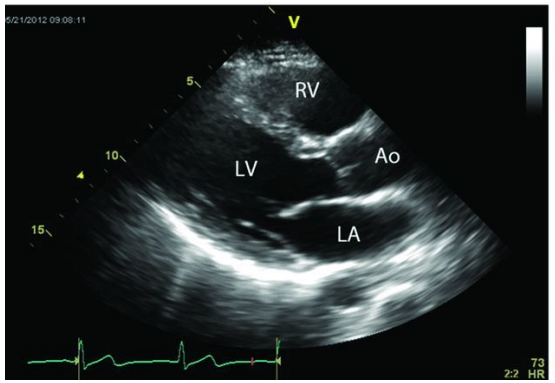
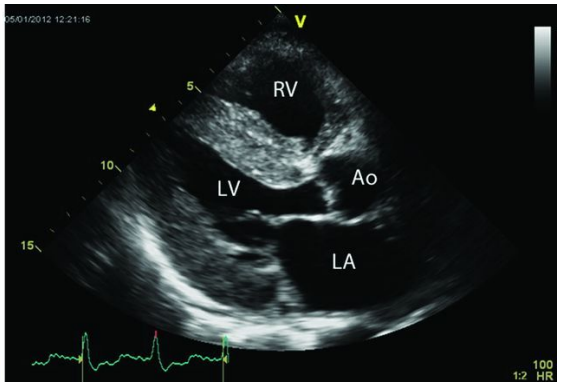


Fig. 3 – Transthoracic echocardiography demonstrating typical morphological findings in patient with amyloid cardiomyopathy: the walls of non-dilated LV are concentrically thickened with increased echogenicity of the myocardium; thickening of RV free wall as well as of both dilated atria and interatrial septum is also seen; considerable thickening of mitral and tricuspid valve cusps is present (apical 4-chamber view) (LV, left ventricle; RV, right ventricle).





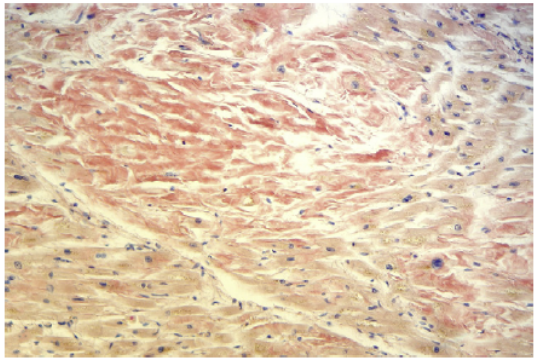


Fig. 1 – Amyloid infiltration of the myocardium (Congo red stain, original magnification × 200).

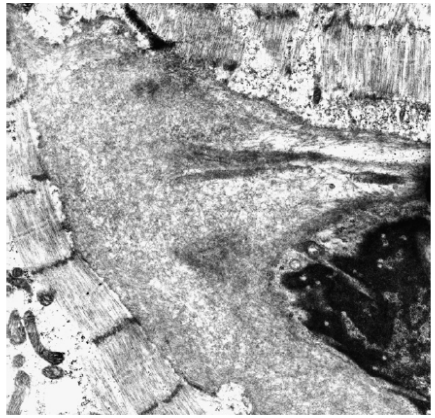
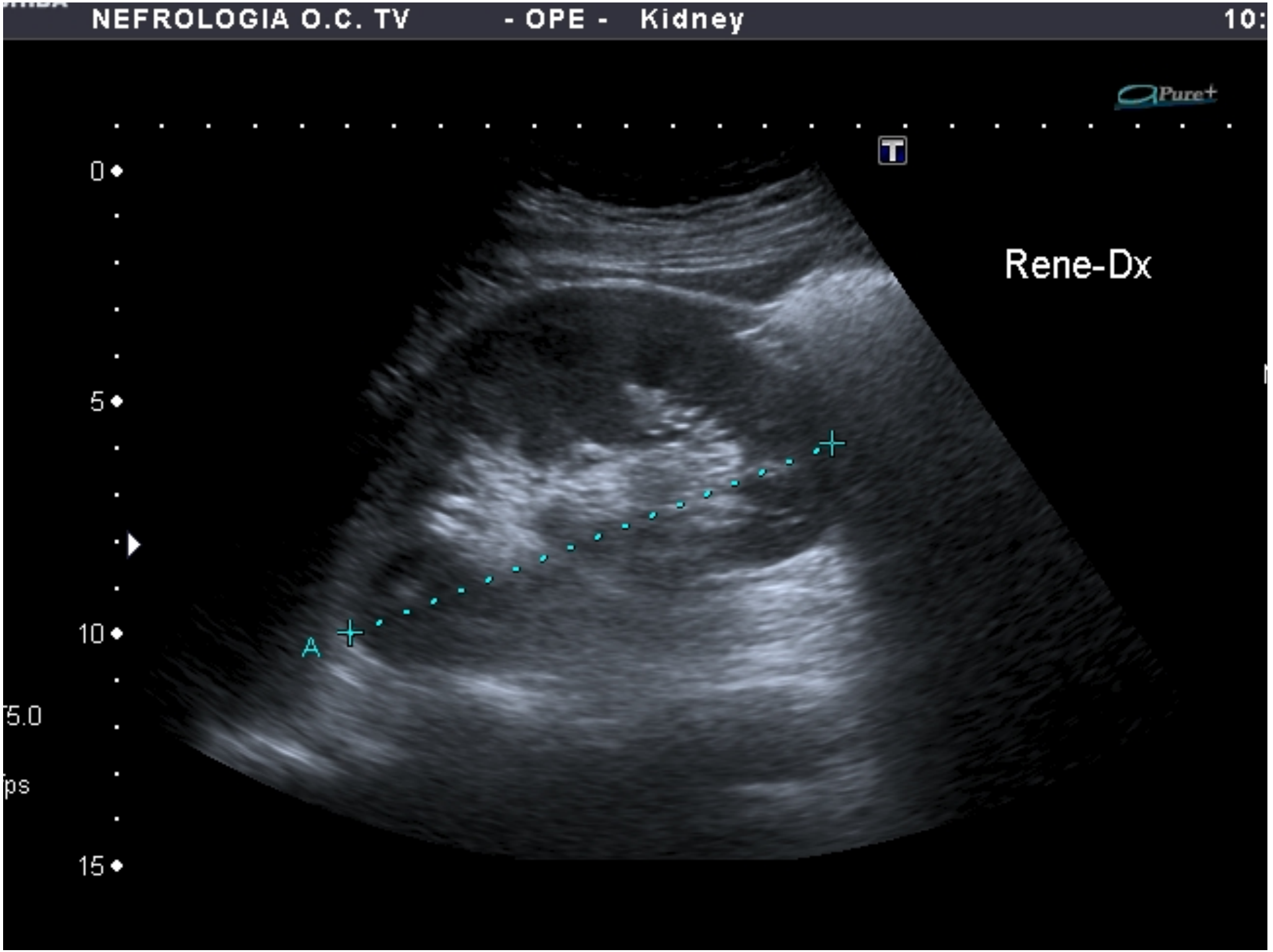


Fig. 2 – Electron microscopy of the myocardial specimen. A mesh formed from randomly oriented amyloid fibrils is located within the myocardium (original magnification × 6000).

Increased echogenicity of thickened ventricular myocardium, also referred to as "granular" or "sparkling" appearance, has been reported in several studies [52–54]. However, this phenomenon can occur in other causes of LV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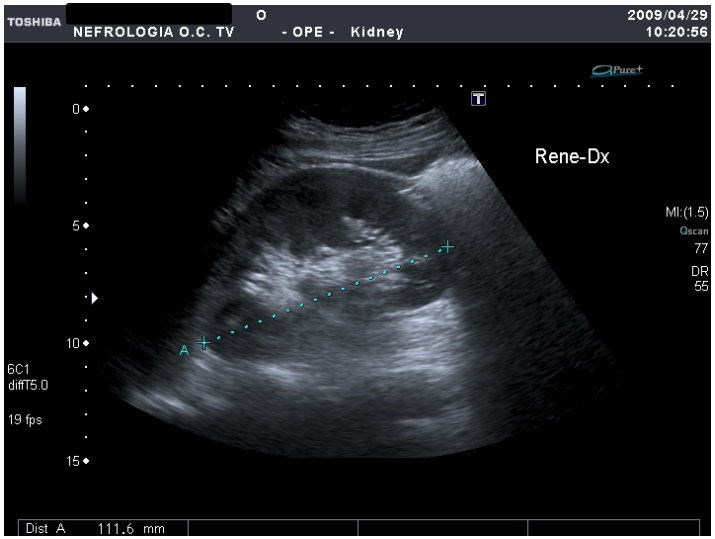
Renal Relevant Radiology: Use of Ultrasonography in Patients with AKI

Sarah Faubel, Nayana U. Patel,† Mark E. Lockhart,‡ and Melissa A. Cadnapaphornchai§*



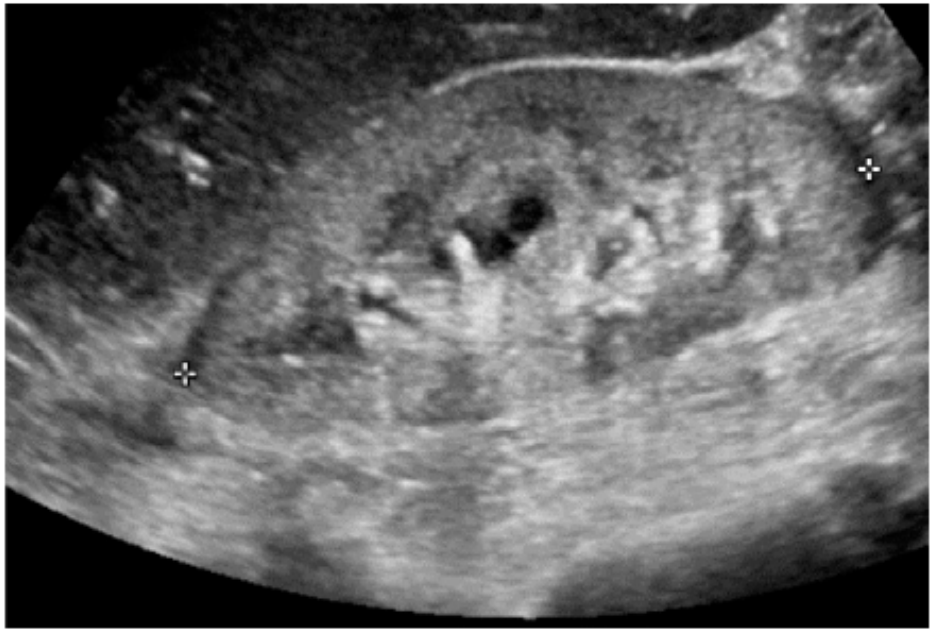
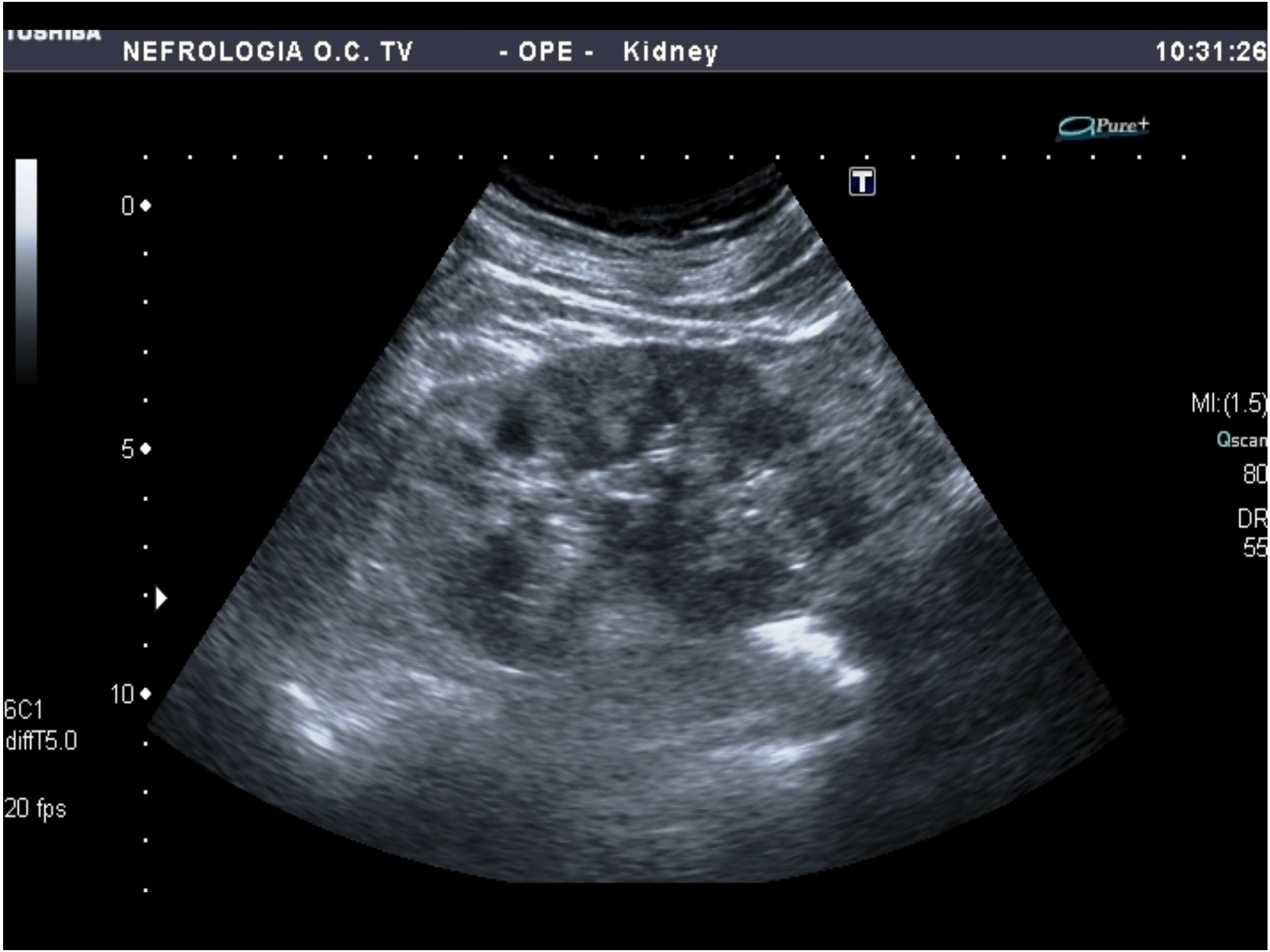


Figure 4. | AKI in a patient with multiple myeloma. Grayscale longitudinal ultrasonographic image of the right kidney demonstrates abnormal bright renal parenchyma in a 39-year-old woman with multiple myeloma and AKI.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MATERIALE INVIATO

Accettato il 04/07/2013

A Biopsia renale

Notizie Cliniche
IR ingravescente (creatinina da 1,3 a 2,7mg/dl) con sindrome nefrosica; prove immunologiche negative, non componente M

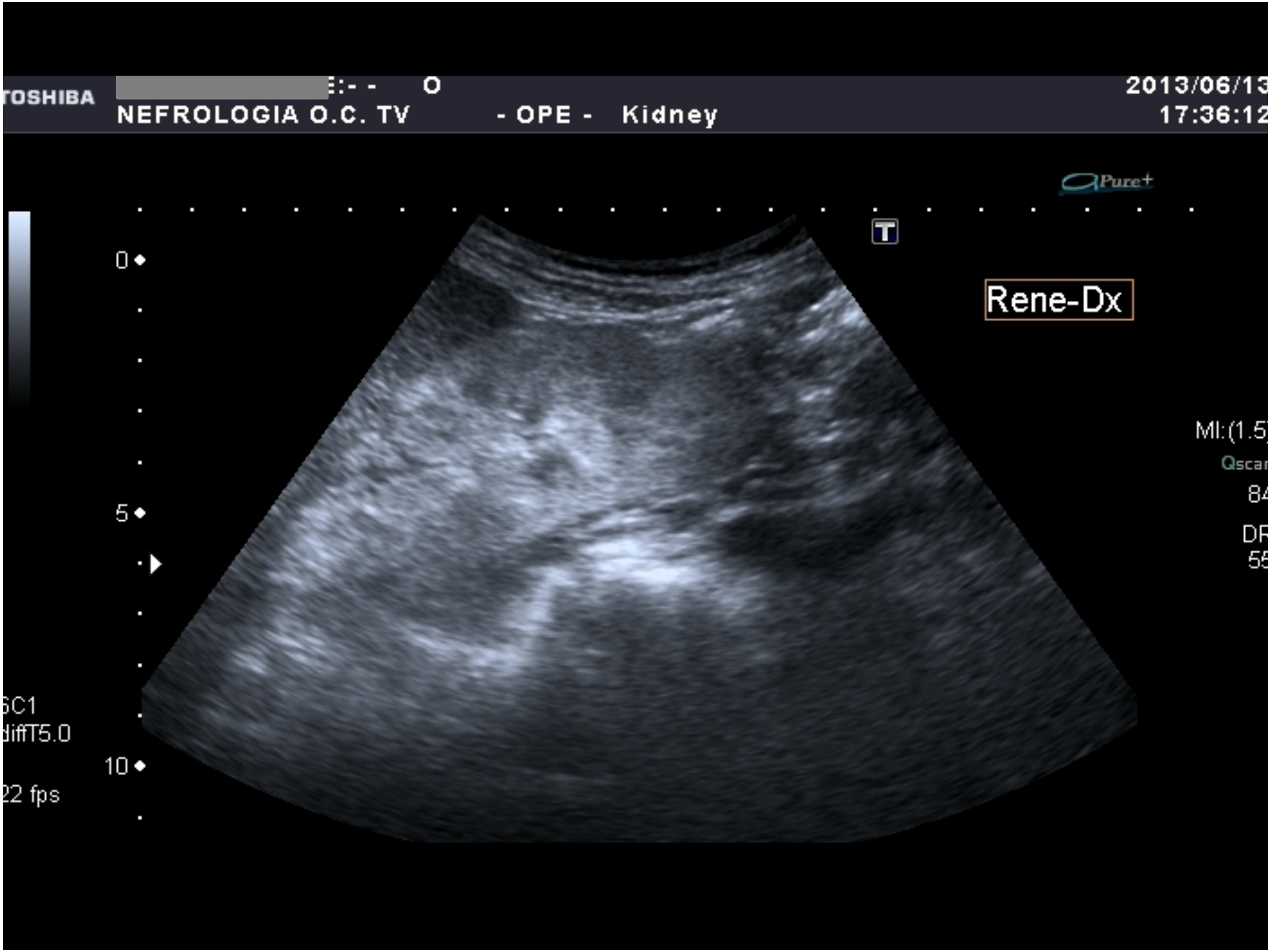
DESCRIZIONE

Frustolo di parenchima renale comprendente fino a 19 glomeruli (9 dei quali ialini) con aree di sclerosi segmentaria del flocculo, più evidenti in prossimità del polo vascolare, raggrinzimento delle membrane basali glomerulari e depositi di materiale similcollagenico nelle porzioni perilari della capsula del Bowman.
Infiltrati infiammatori linfoplasmacitari di moderata intensità irregolarmente distribuiti e atrofia tubulare di grado moderato-severo
Con la colorazione PAS metenamina si evidenziano depositi negativi intraparietali a carico dei vasi.
Positiva la ricerca di amiloide con metodica rosso Congo a carico dei vasi e dei glomeruli

Immunofluorescenza:
depositi granulari aspecifici per C3, G,M, kappa e lambda

DIAGNOSI

Quadro istologico coerente con amiloidosi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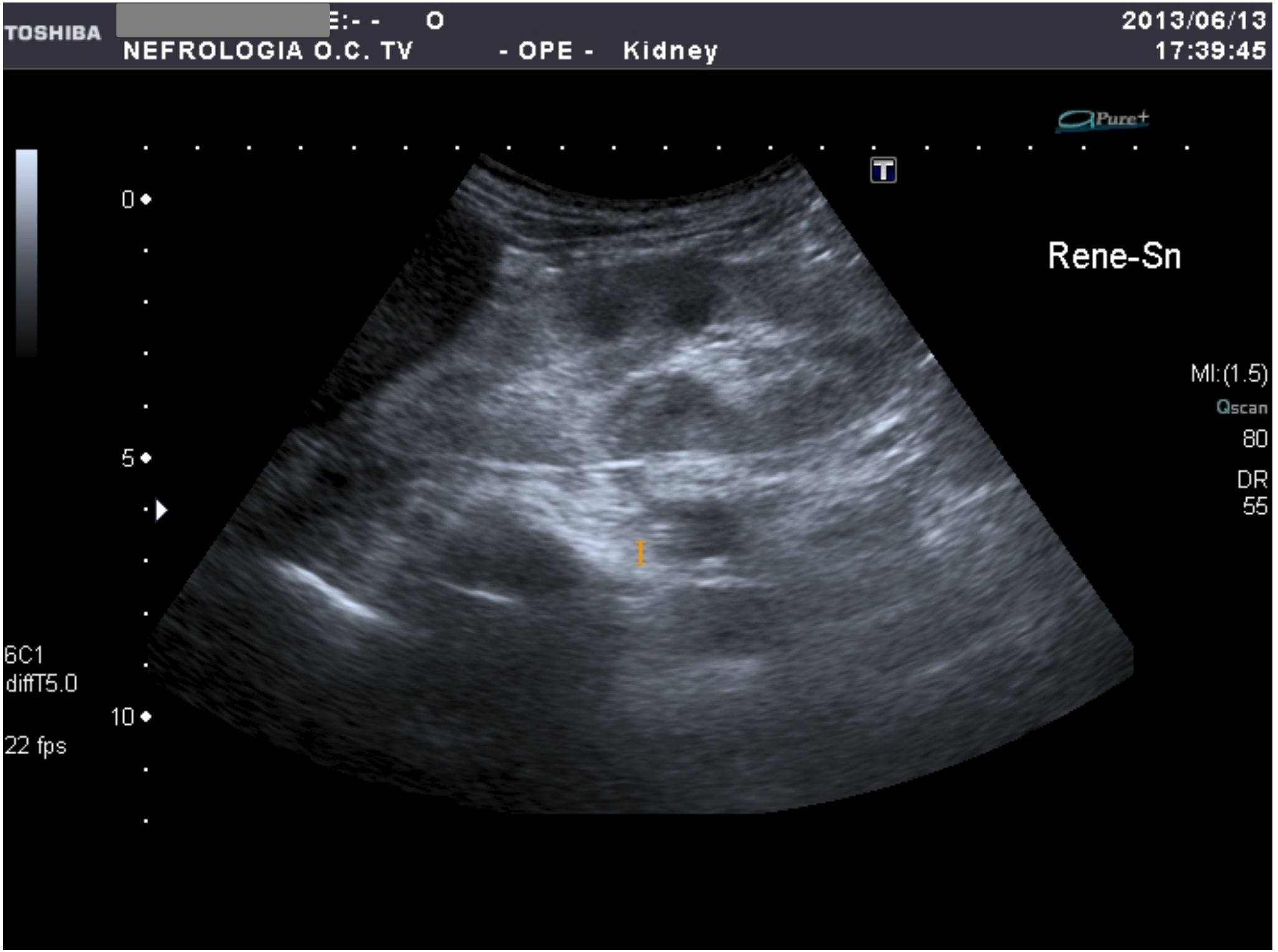
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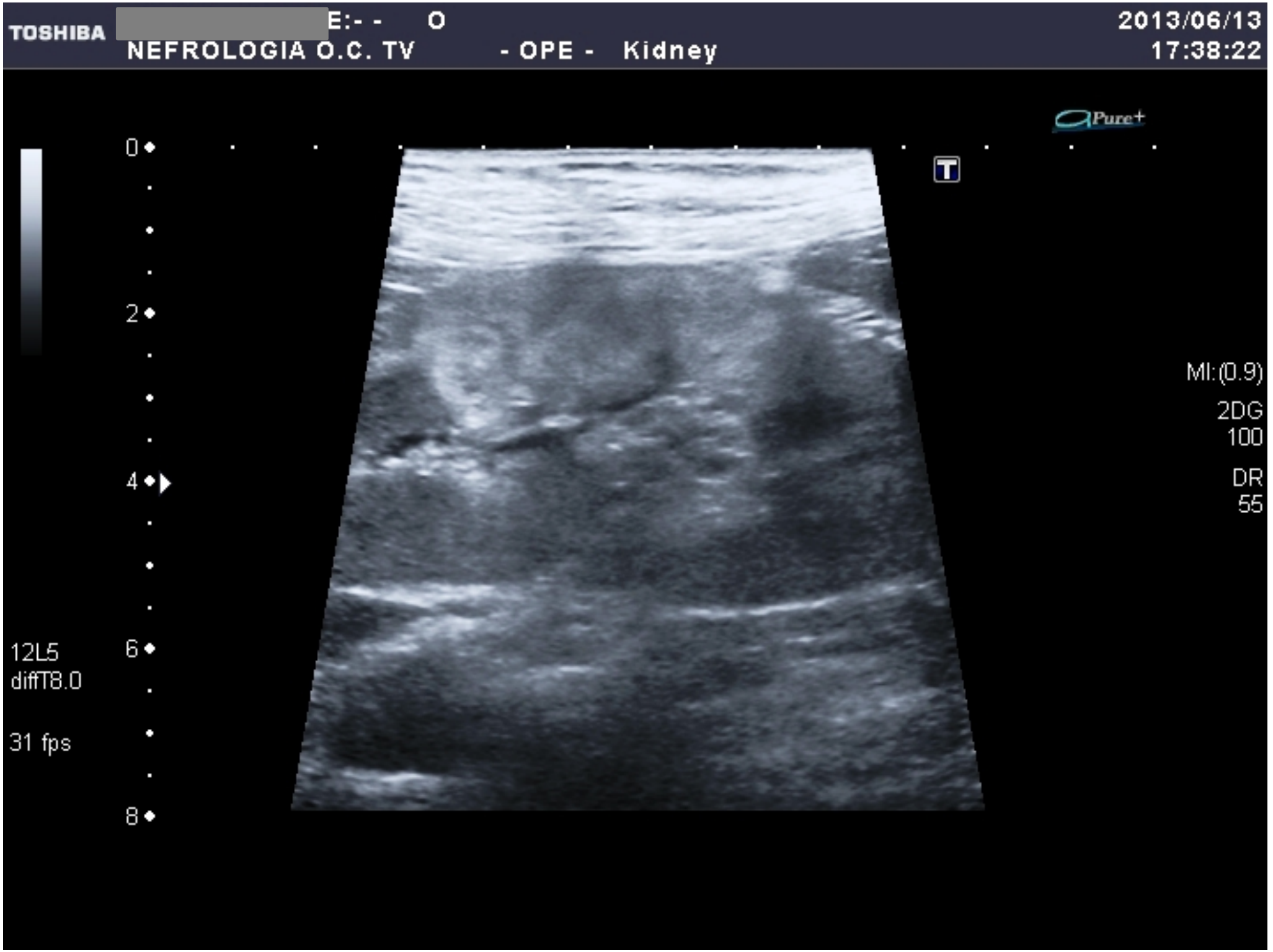
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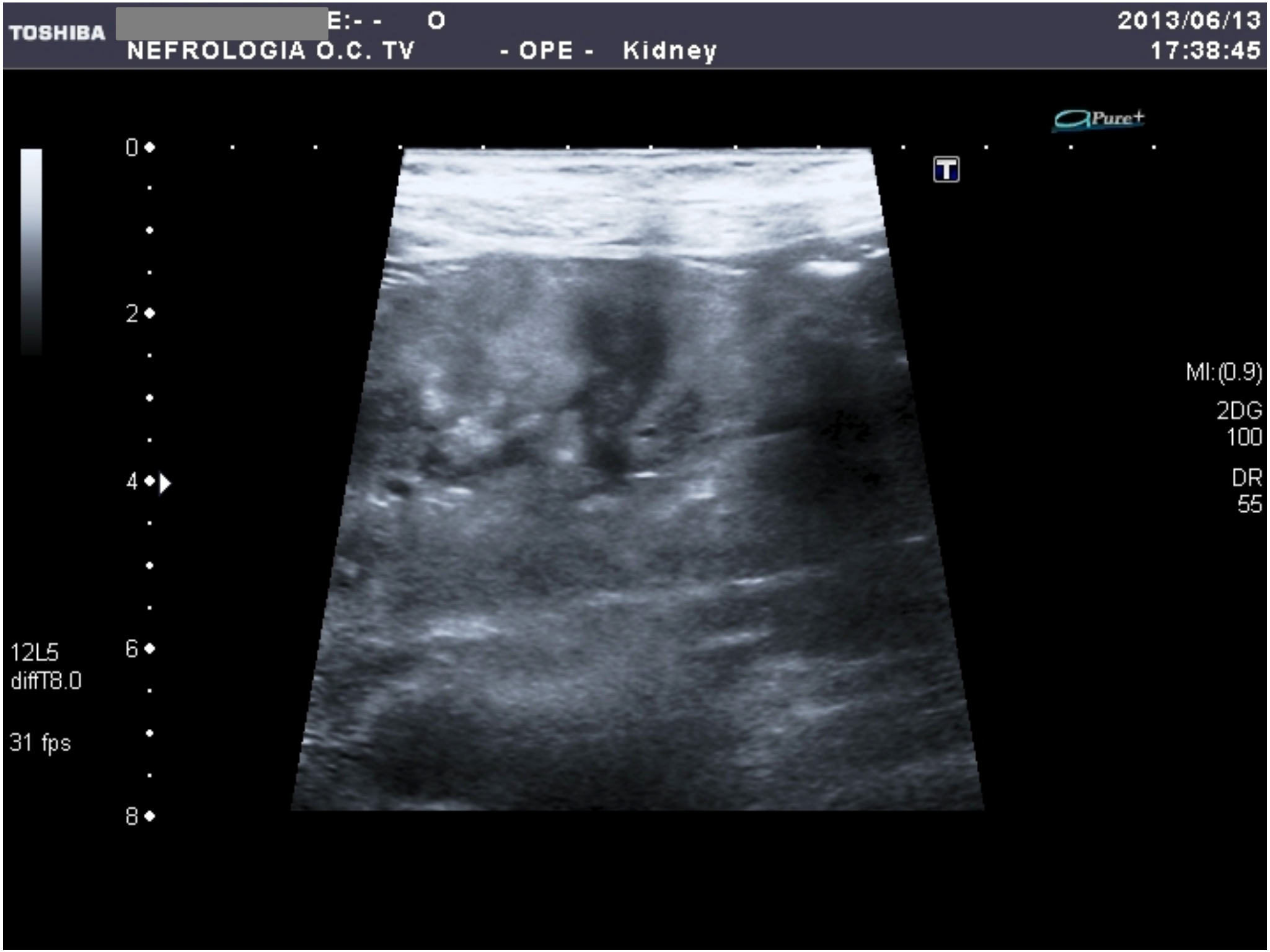
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MATERIALE INVIATO

Accettato il 17/06/2013

A Biopsia rene sx

Notizie Cliniche
IRA con sindrome nefrosica (creatininemia 6mg/dl, proteinuria 6-8g/die); componente monoclonale IgG lambda

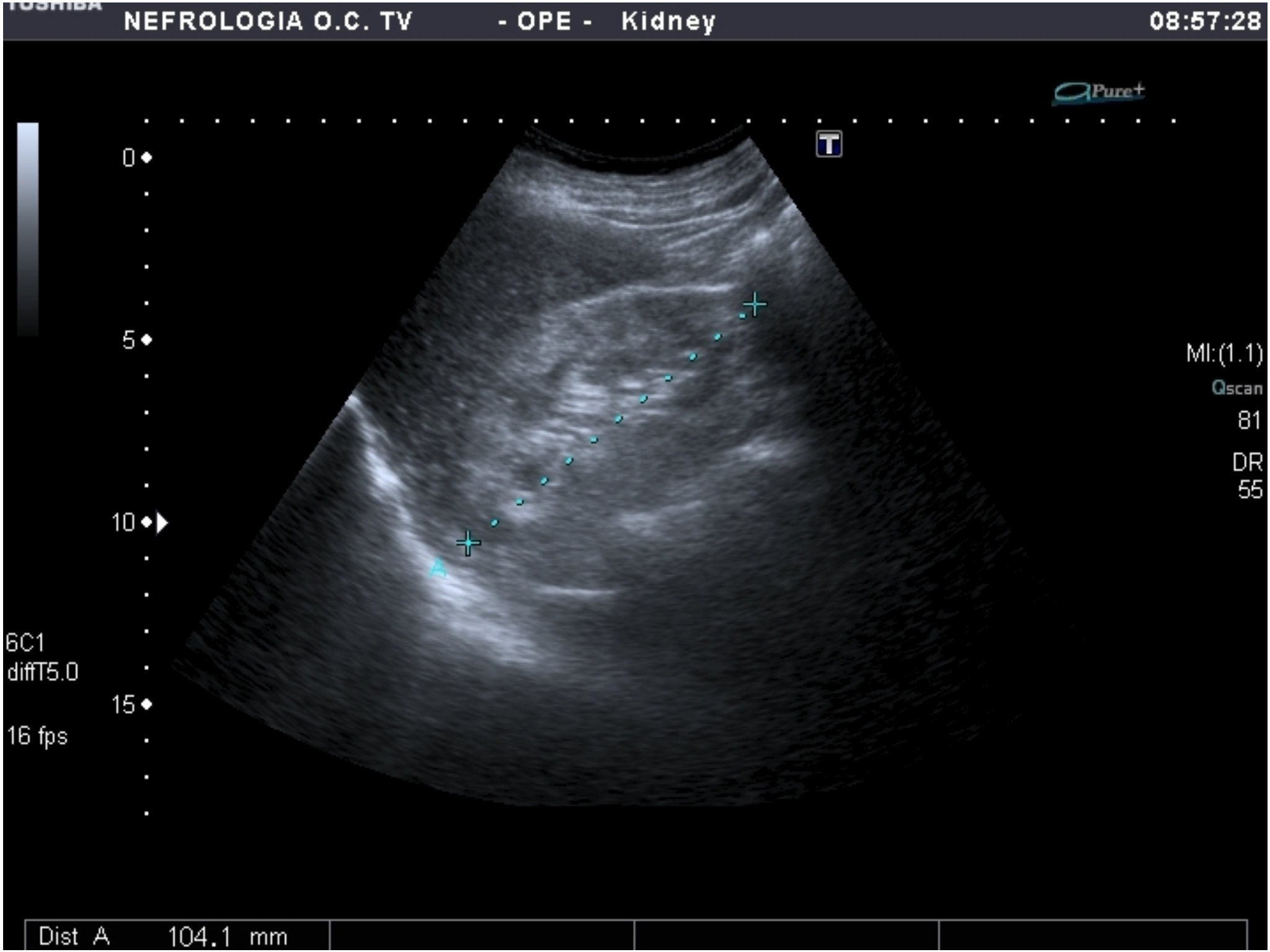
DESCRIZIONE

Frustolo di parenchima renale comprendente 10 glomeruli ad architettura sovvertita per la presenza di grossolani depositi debolmente PAS positivi nodulari.
Atrofia tubulare di grado moderato; depositi amorfi interstiziali
Vasi ispessiti con depositi paietali di materiale amorfo.
Positiva la ricerca di amiloide con metodica rosso Congo

Immunofluorescenza: positività diffusa per catena leggera lambda in sede glomerulare e perivascolare

DIAGNOSI

Quadro coerente con amiloidosi renale


NEFROLOGIA O.C. TV - OPE - Kidney
08:57:28
Pure+
0
5
10
15
MI:(1.1)
Qscan
81
DR
55
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diffT5.0
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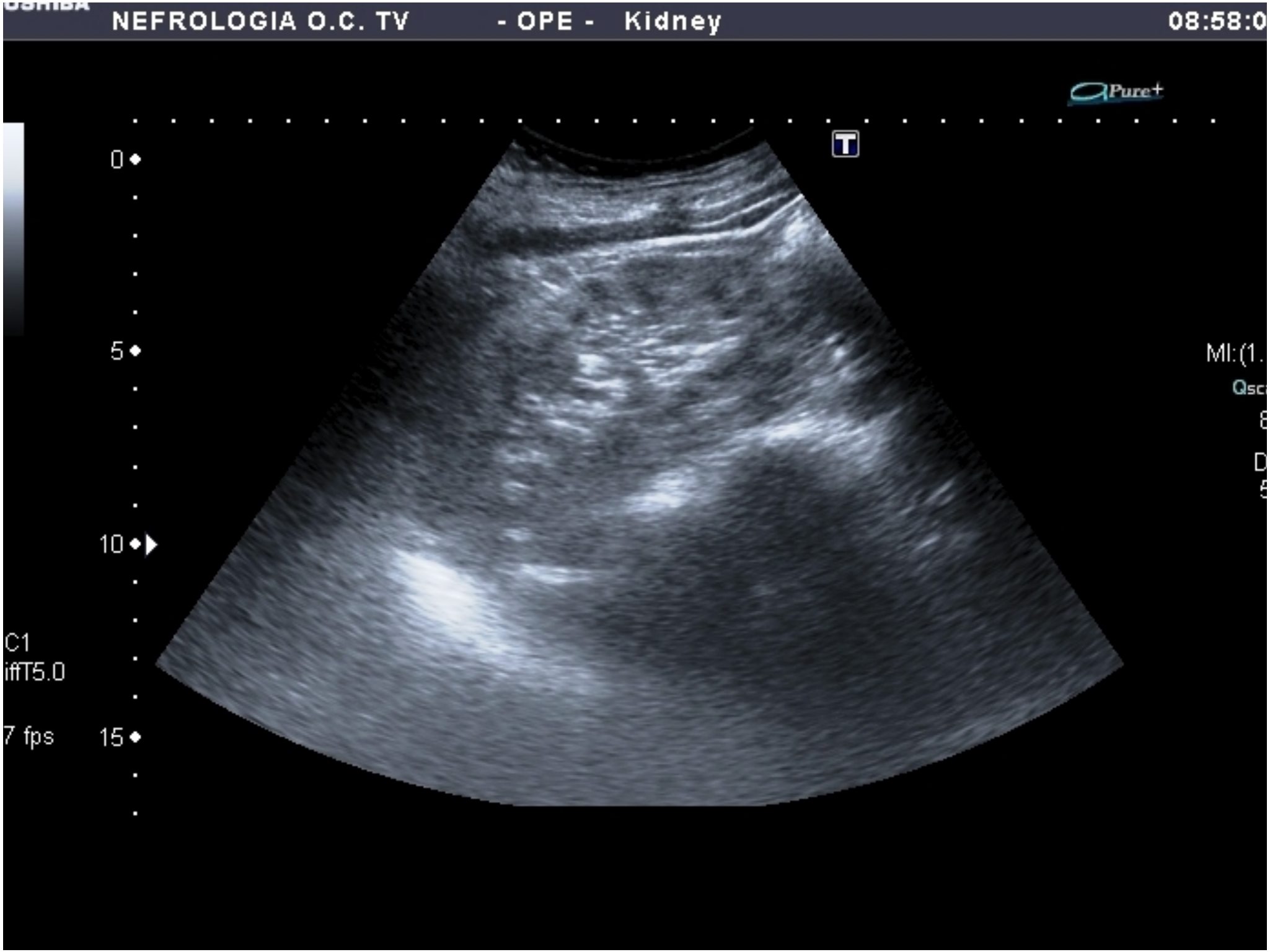
Dist A 104.1 mm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Kidney
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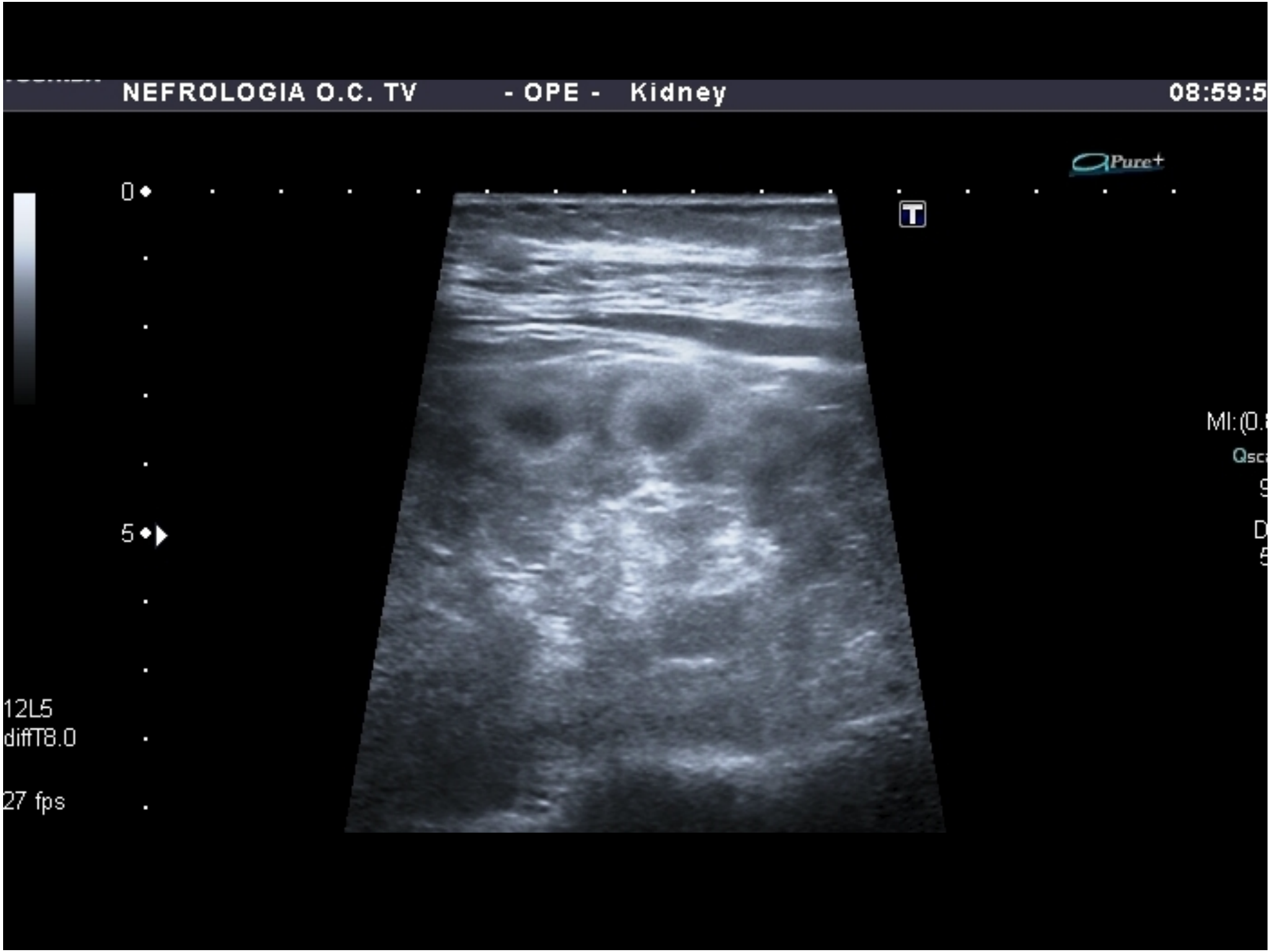
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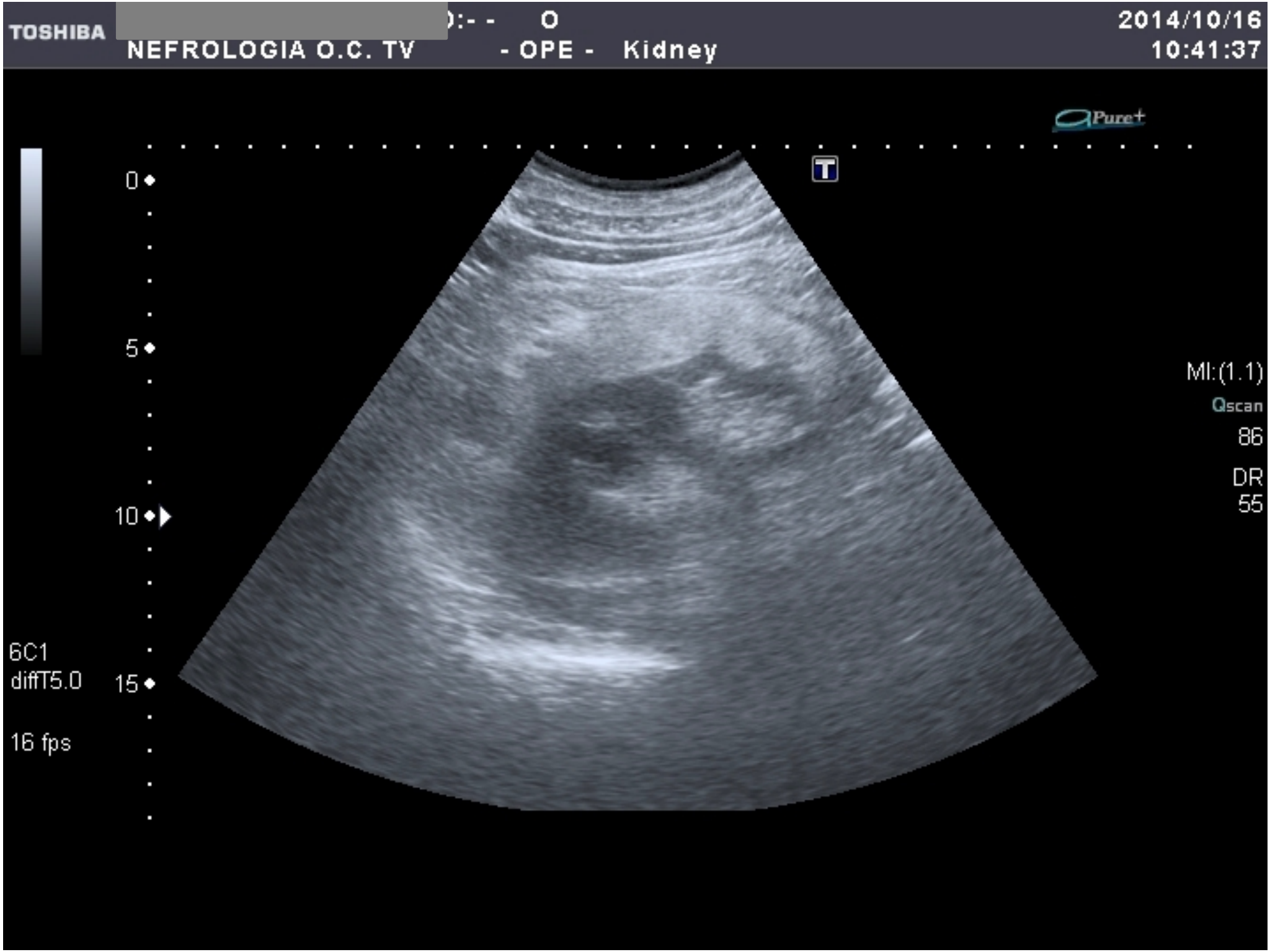
Pure+
0
5
MI:(0.
Qsc
12L5
diffT8.0
27 fps

MATERIALE INVIATO

A Biopsia antro angulus gastrico
B Rilevatezze antrali
C Biopsia corpo gastrico
D Polipo del corpo

DIAGNOSI

A,B- Frammenti bioptici di mucosa gastrica con fibrosi e deposito di amiloide nel corion. Negativa la ricerca per HP.
C- Frammenti bioptici di mucosa gastrica con struttura istologica nei limiti della norma. Negativa la ricerca per HP.
D- Frammento di polipo ghiandolare del corpo gastrico.


TOSHIBA
NEFROLOGIA O.C. TV
- OPE - Kidney
2014/10/16
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0
5
10
15
MI:(1.1)
Qscan
86
DR
55
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diffT5.0
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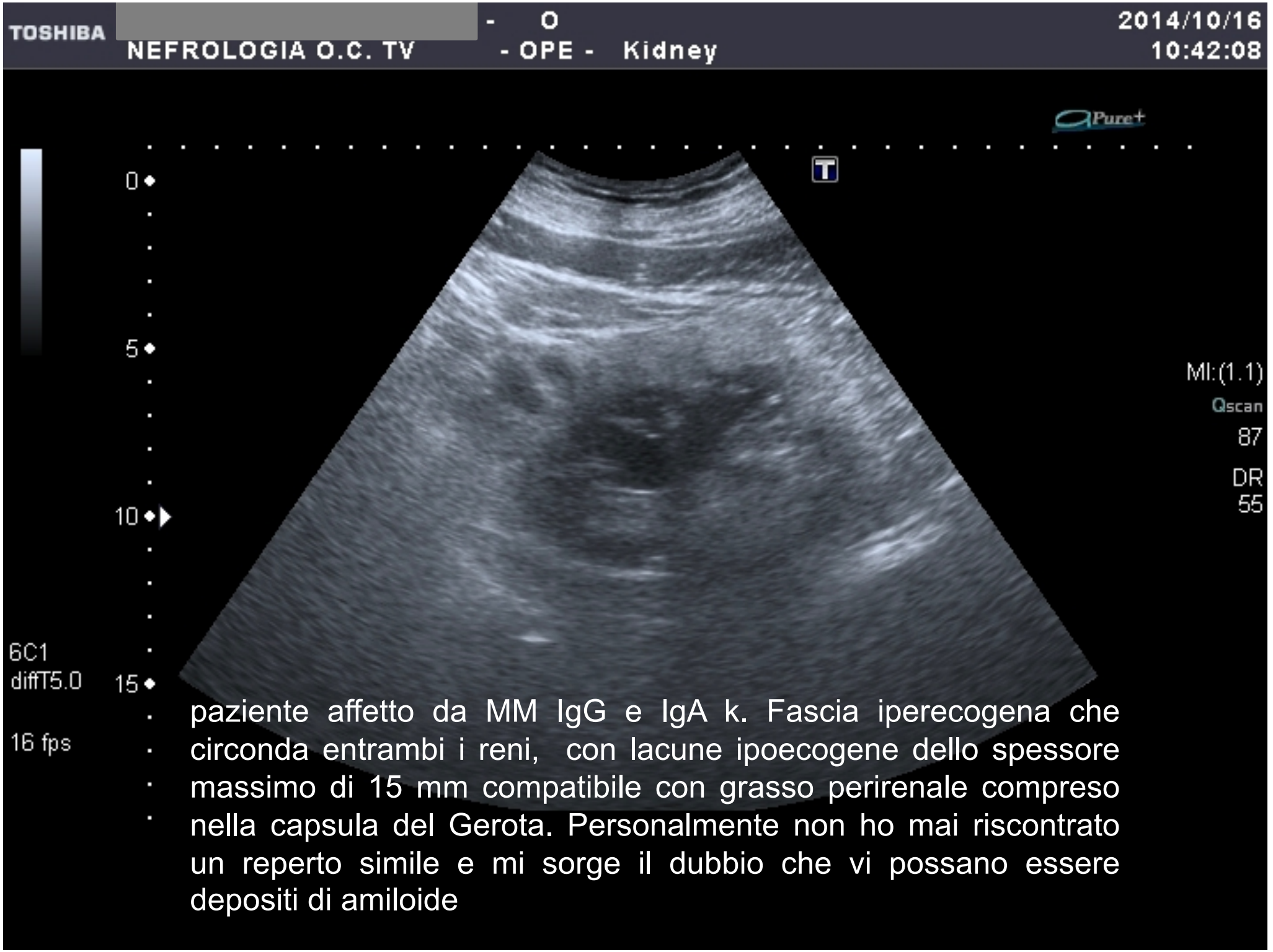
TOSHIBA
NEFROLOGIA O.C. TV
- O
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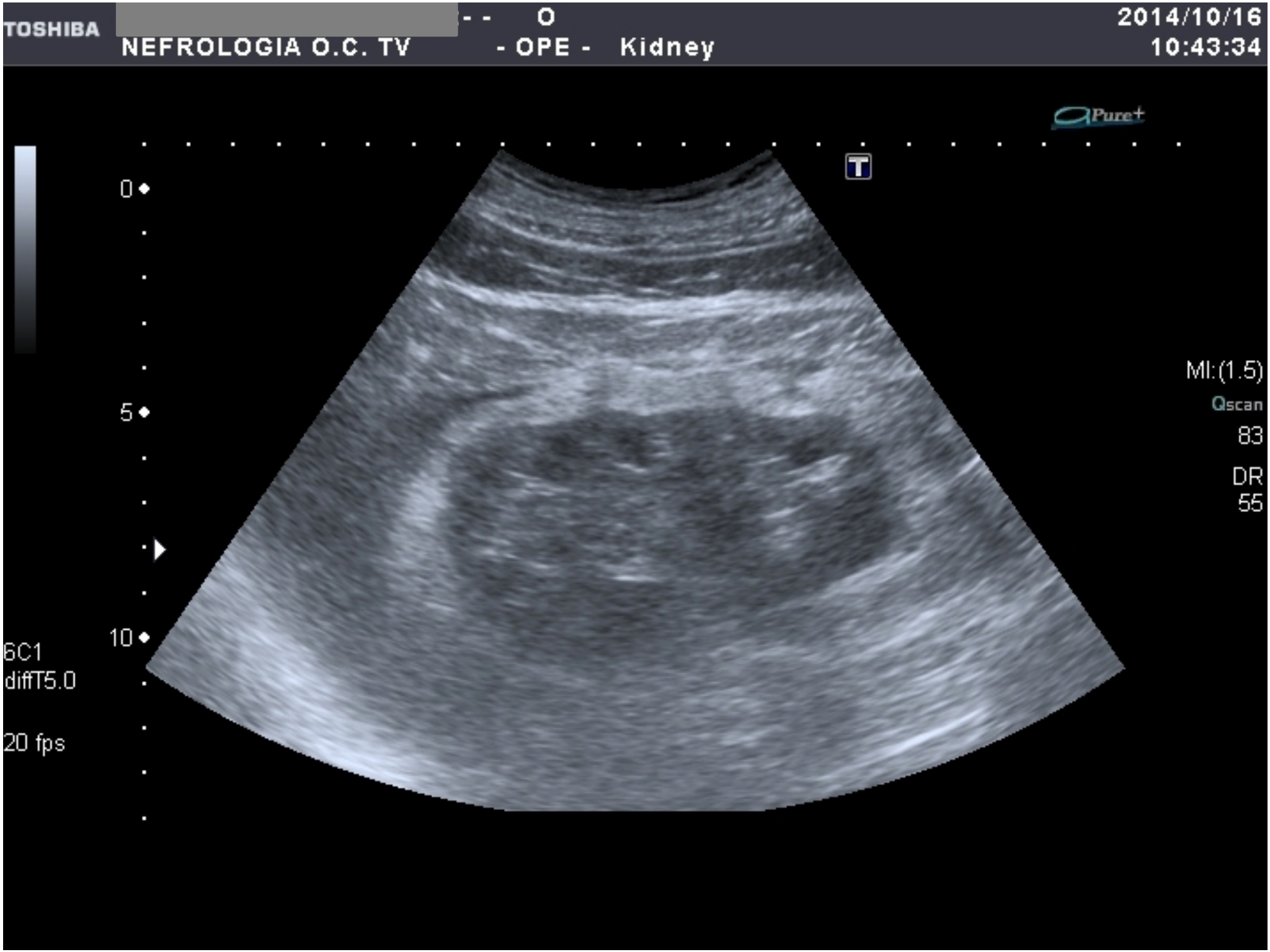
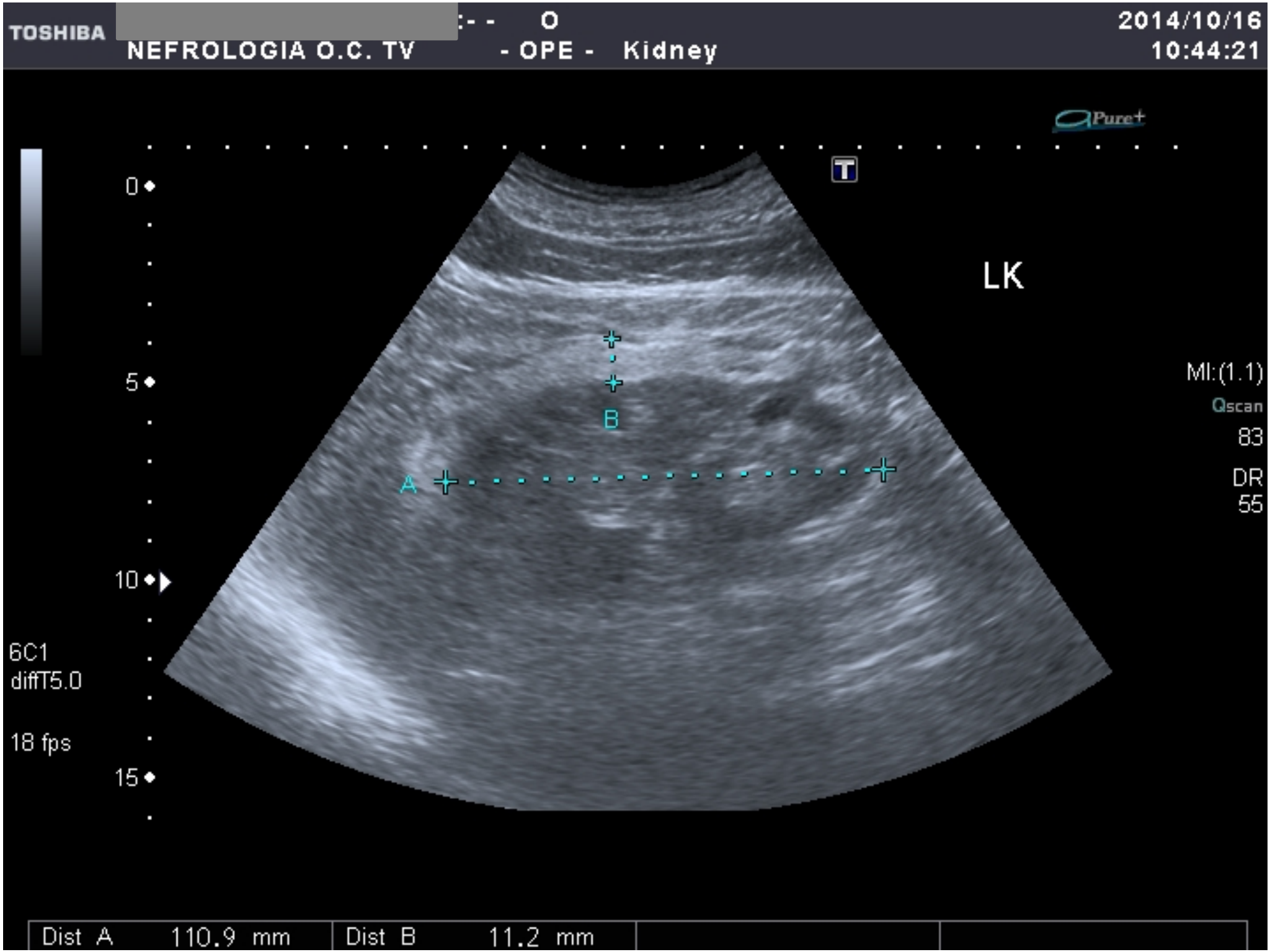
2014/10/16
10:42:08
Pure+
0
5
10
15
MI:(1.1)
Qscan
87
DR
55
6C1
diffT5.0
16 fps
paziente affetto da MM IgG e IgA k. Fascia iperecogena che circonda entrambi i reni, con lacune ipoecogene dello spessore massimo di 15 mm compatibile con grasso perirenale compreso nella capsula del Gerota. Personalmente non ho mai riscontrato un reperto simile e mi sorge il dubbio che vi possano essere depositi di amiloide


TOSHIBA
NEFROLOGIA O.C. TV
- - O
- OPE - Kidney
2014/10/16
10:43:34
Pure+
T
0
5
10
MI:(1.5)
Qscan
83
DR
55
6C1
diffT5.0
20 fps


TOSHIBA
NEFROLOGIA O.C. TV
- OPE - Kidney
2014/10/16
10:44:21
Pure+
LK
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Qscan
83
DR
55
6C1
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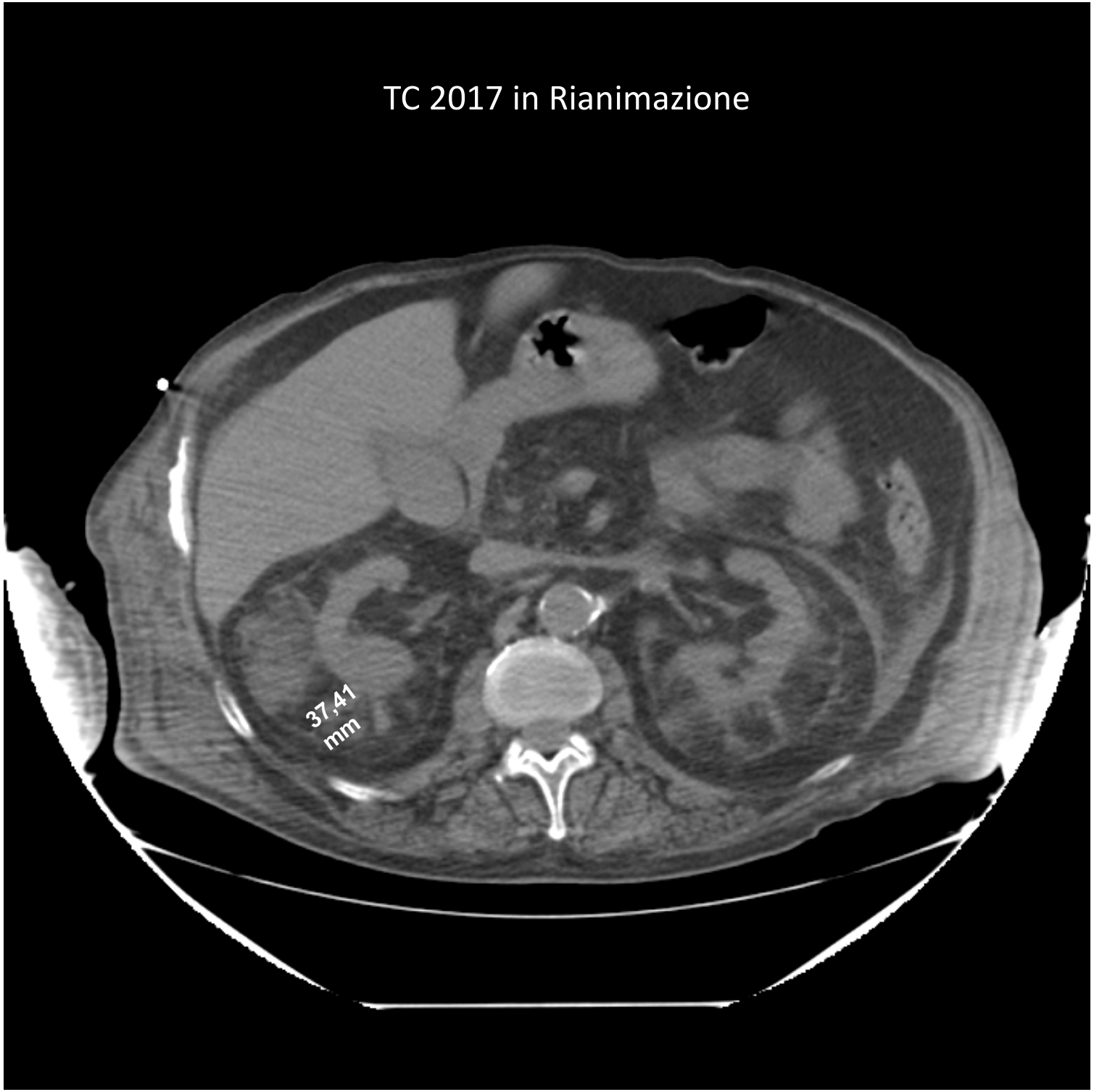
18 fps
Dist A 110.9 mm
Dist B 11.2 mm


TC 2017 in Rianimazione
37,41
mm

Esame

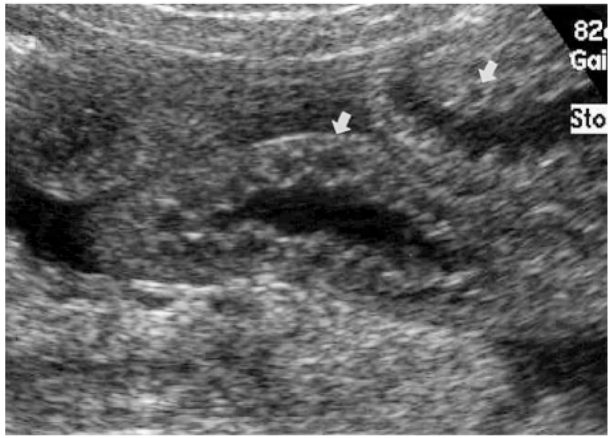
TAC ADDOME COMPLETO CON MDC 30/03/2017 09:05

Esame eseguito in urgenza e gravato da artefatti.

Falda liquida periepatica e pericolecistica perisplenica scende lungo le docce parieto-coliche fino in piccolo bacino. Imbibiti i tessuti adiposi retroperitoneali in particolare in regione presacrale.
Fegato di dimensioni aumentate con morfologia conservata grossolanamente disomogeneo presenta alcune sfumate areole ipodense, la maggiore alla cupola di circa 13 mm di diametro meglio riconoscibili nella fase portale dell'esame, possibili angiomi atipici.
Colecisti distesa contiene bile densa e piccole formazioni litiasiche.
Non dilatate le vie biliari intra ed extra epatiche.
Milza nei limiti.
Aspetti marcatamente involutivi del pancreas.
Surreni nei limiti.
Reni in sede di dimensioni ai valori inferiori di norma in particolare quello di sinistra, con netto assottigliamento dello spessore corticale, entrambi presentano alcune formazioni rotondeggianti ipodense con aspetto cistico la maggiore parapielica destra di circa 24 mm di diametro.
Bilateralmente il tessuto adiposo pararenale appare marcatamente addensato con addensamento dei setti mesorenali e nel suo contesto si riconoscono multiple nodulazioni solide più evidenti a destra ove la maggiore presenta diametro di almeno 30 mm, alcune di esse con scarsi piani di clivaggio con il parenchima renale.
Non calico-pielectasie.
Non dilatazioni aneurismatiche dell'aorta addominale che presenta calcificazioni di parete.
Diverticolosi del sigma, contratto.
Vescica pressoché depleta contenente catetere di Foley.
Prostata di dimensioni conservate.
Colestasi di passanti per la cupola epatica;
Versamento pleurico basale bilaterale più evidente a destra ove raggiunge spessore massimo di circa 18 mm con addensamento parenchimale consensuale.

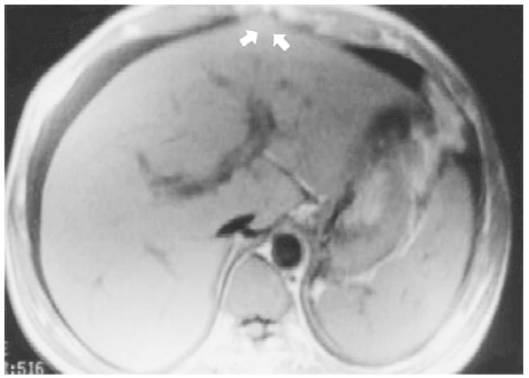
Abdominal Amyloidosis: Spectrum of Radiological Findings

S. H. KIM*,†, J. K. HAN‡, K. H. LEE*,†, H. J. WON*,†, K. W. KIM*,†, J. S. KIM*,†, C. H. PARK*,†, B. I. CHOI‡

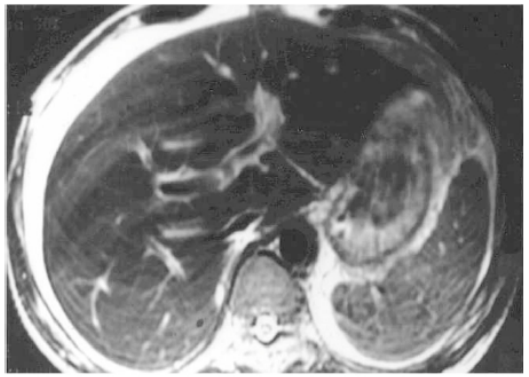


(*b*)

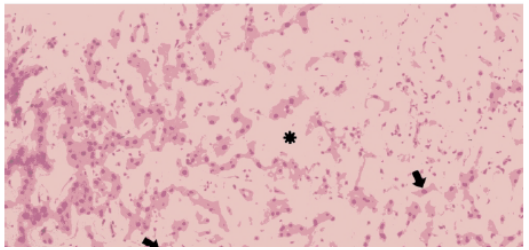
Fig. 6 – "Target sign" in the bowel of a 70-year-old man with multiple myeloma. (*a*) CT demonstrating diffuse and even wall thickening with a double halo, the so called "target sign", in the small (arrows) and large bowel (open arrow). (*b*) Ultrasound image showing diffuse thickening of the jejunal loop with ascites (arrows). In this patient, CT angiography (not shown) was performed and it revealed no large vessel compromise, suggesting ischaemic bowel disease. Colonoscopy (not shown) revealed granular and nodular mucosa with atrophic change in the colon. Diffuse amyloid infiltration was found in a subsequent colonic biopsy.

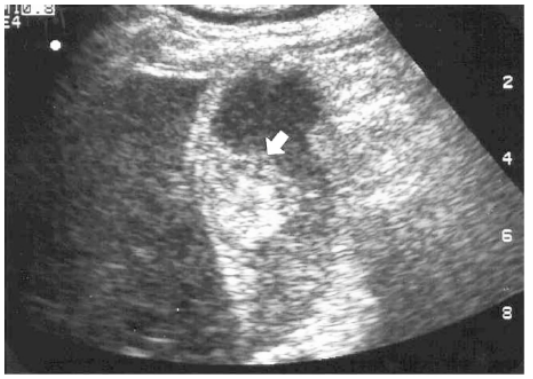


(*a*)

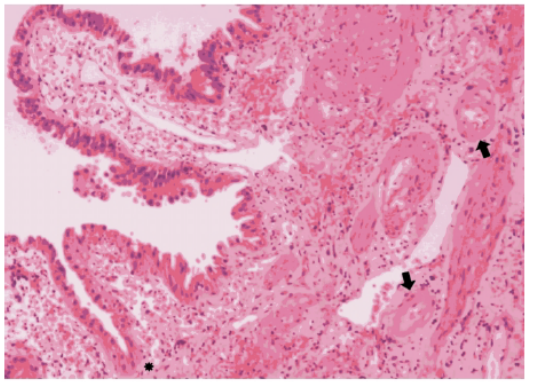


(*b*)





(*a*)



(*b*)

Fig. 10 – Gallbladder amyloidosis in a 68-year-old man with pulmonary tuberculosis. He complained of sudden onset right upper quadrant pain. (*a*) Ultrasonogram shows mild wall thickening of the gallbladder and dirty pericholecystic infiltration without definite evidence of stone. A focal echogenic mass is also seen in the body of the gallbladder (arrow). The patient was preoperatively diagnosed as having acute acalculous cholecystitis and underwent emergency cholecystectomy. (*b*) Microscopic finding (haematoxylin and eosin stain; original magnification, × 100) reveals acute suppurative cholecystitis with amorphous eosinophilic amyloid deposition in the lamina propria (*) and around small arterioles (arrows) in the submucosa.

Abdominal Amyloidosis: Spectrum of Radiological Findings

S. H. KIM*,†, J. K. HAN‡, K. H. LEE*,†, H. J. WON*,†, K. W. KIM*,†, J. S. KIM*,†, C. H. PARK*,†, B. I. CHOI‡

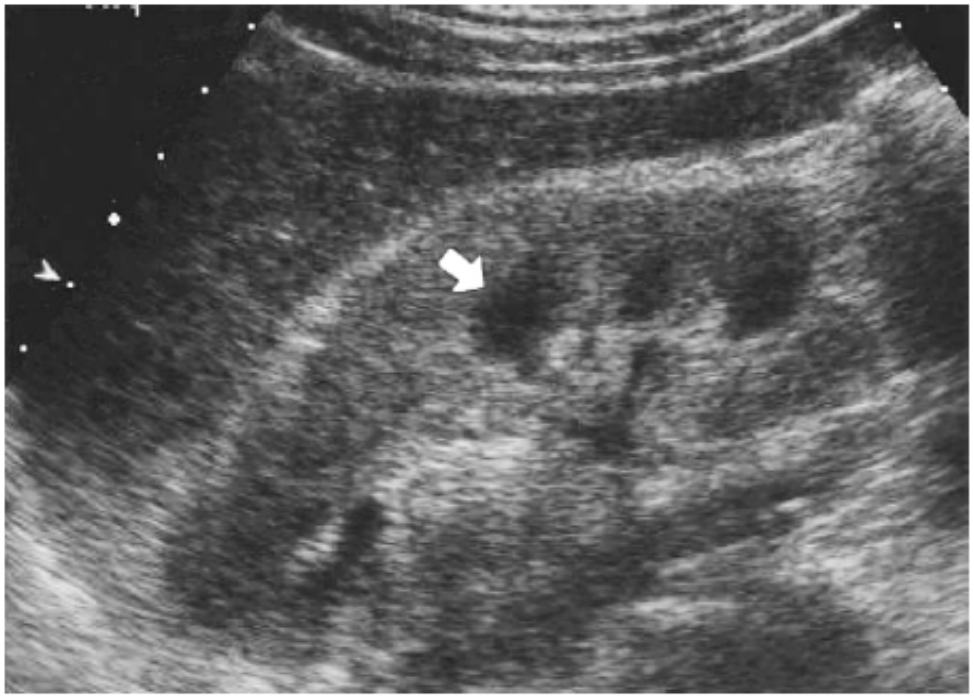
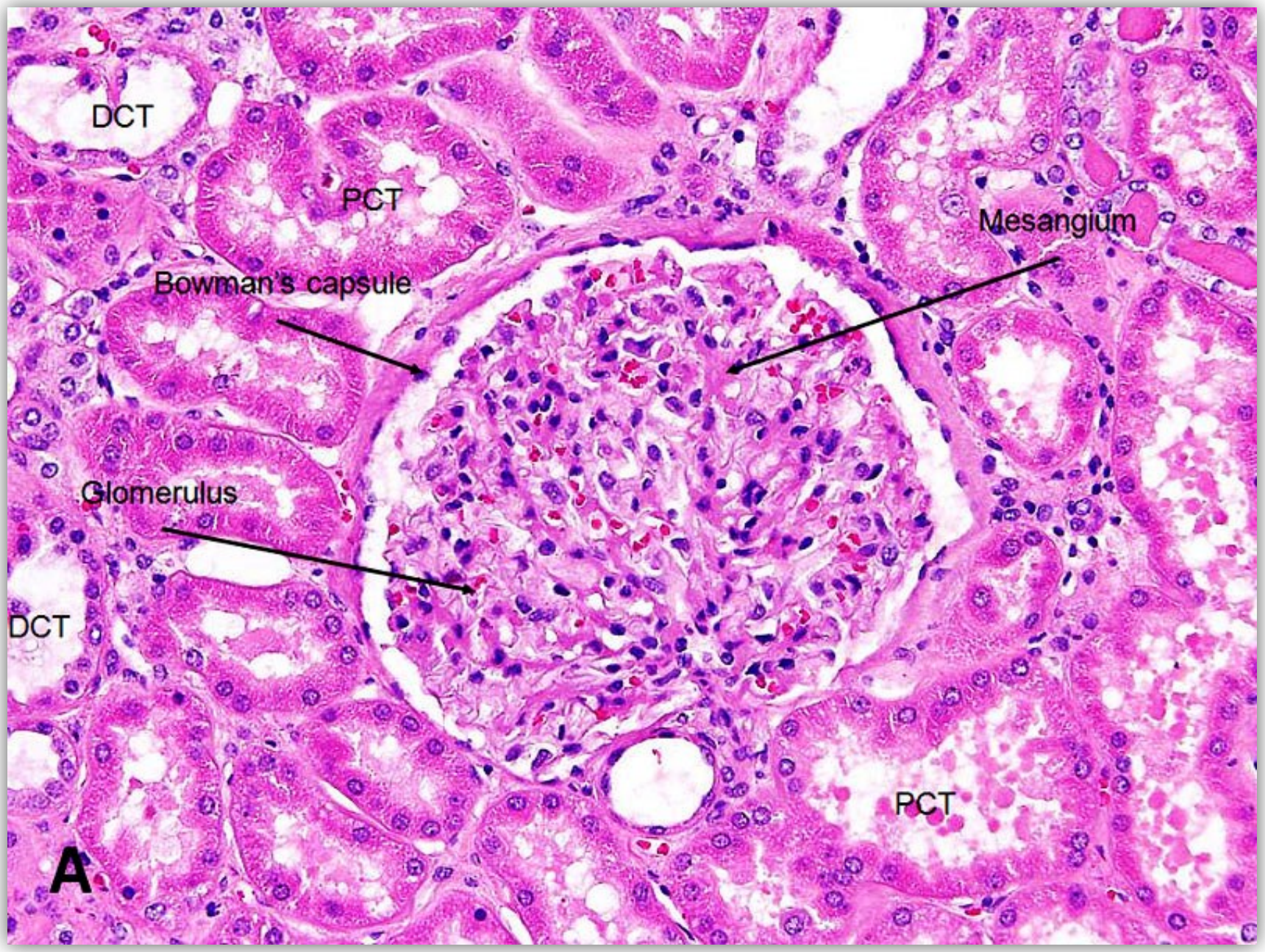


Fig. 11 – Primary renal amyloidosis in a 68-year-old-man. Renal ultrasound shows that the echogenicity of the renal cortex is brighter than that of the liver, and corticomedullary differentiation is accentuated (arrow).


DCT
PCT
Mesangium
Bowman's capsule
Glomerulus
DCT
PCT
A

CONSENSUS
STATEMENT

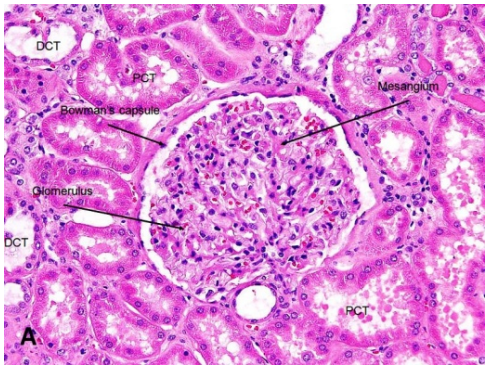
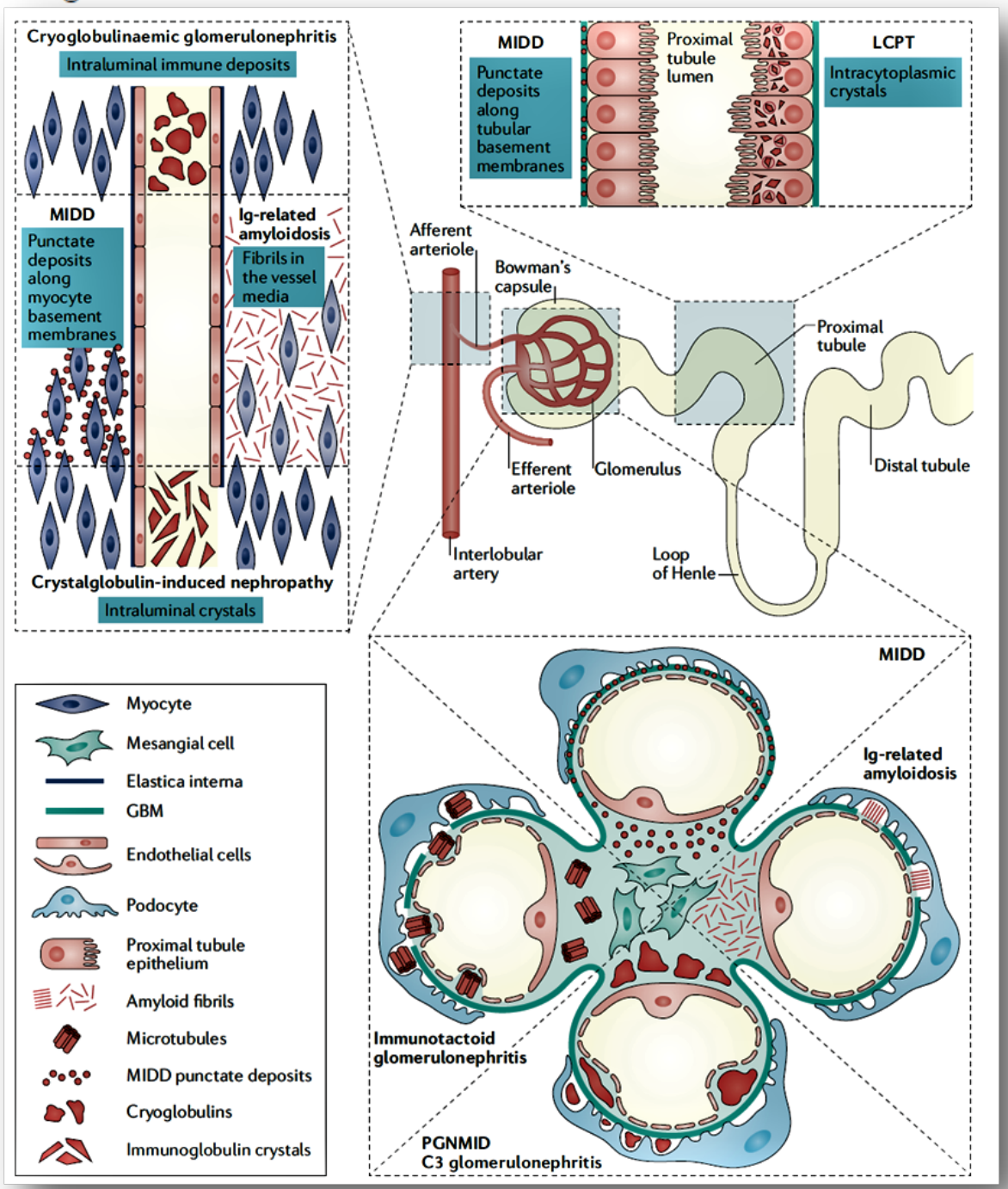
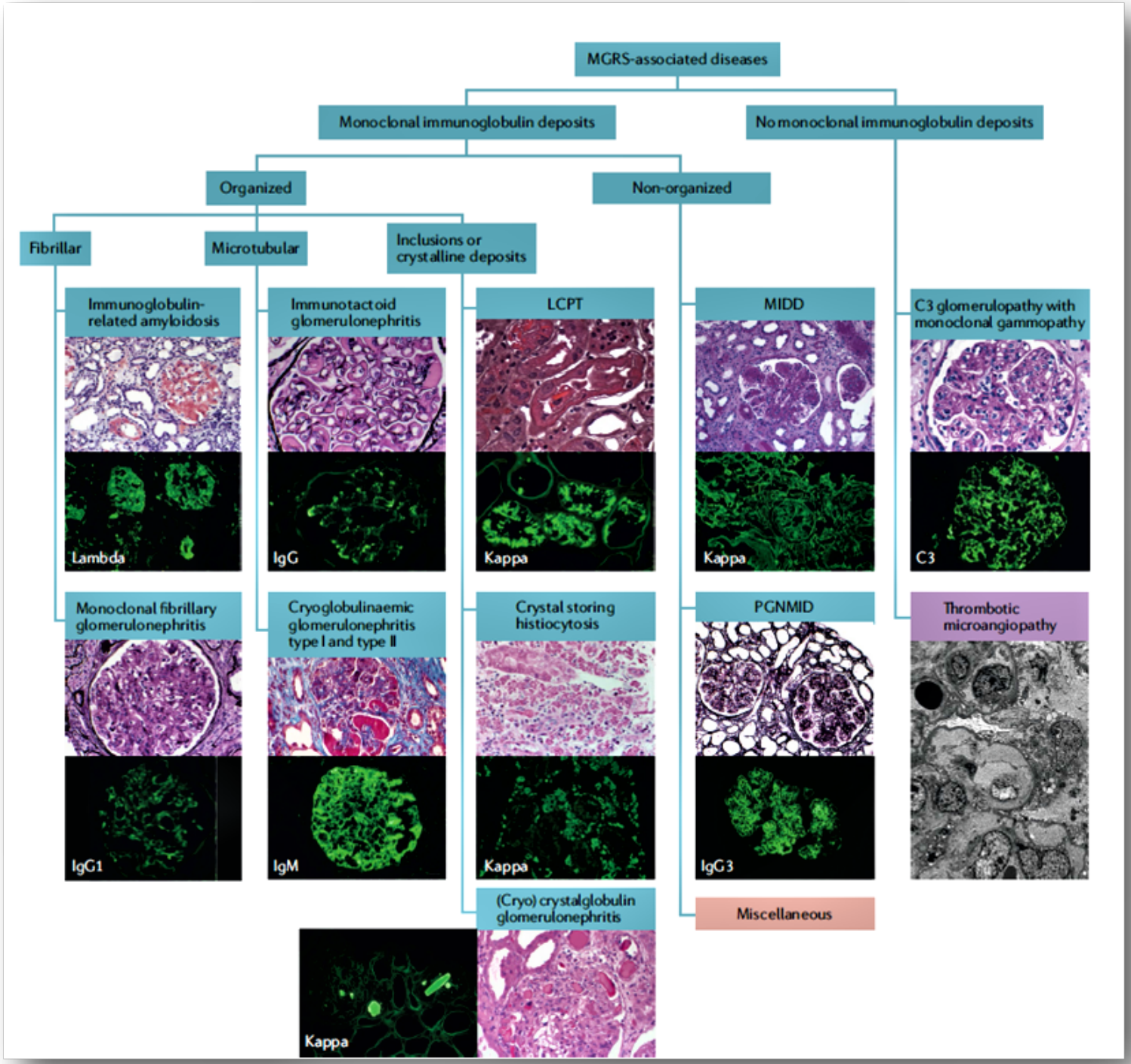


Fig. 1 | **Localization of MGRS-associated renal lesions.**




MGRS-associated diseases
Monoclonal immunoglobulin deposits
No monoclonal immunoglobulin deposits
Organized
Non-organized
Fibrillar
Microtubular
Inclusions or crystalline deposits
Immunoglobulin-related amyloidosis
Lambda
Immunotactoid glomerulonephritis
IgG
LCPT
Kappa
MIDD
Kappa
C3 glomerulopathy with monoclonal gammopathy
C3
Monoclonal fibrillary glomerulonephritis
IgG1
Cryoglobulinaemic glomerulonephritis type I and type II
IgM
Crystal storing histiocytosis
Kappa
PGNMID
IgG3
Thrombotic microangiopathy
(Cryo) crystalglobulin glomerulonephritis
Kappa
Miscellaneous

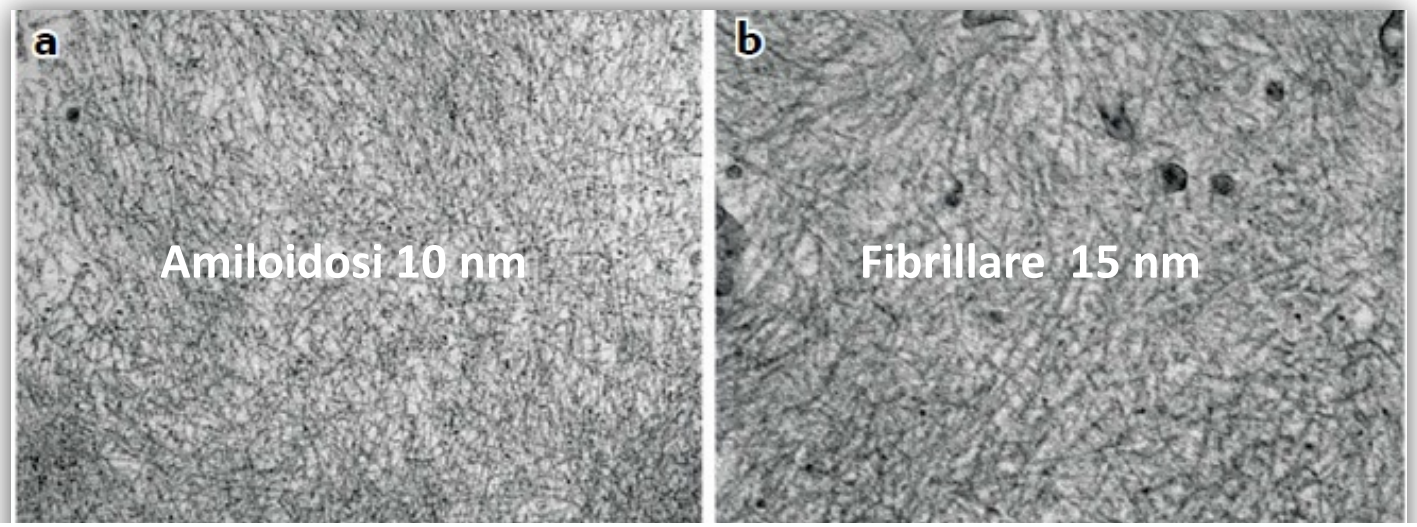
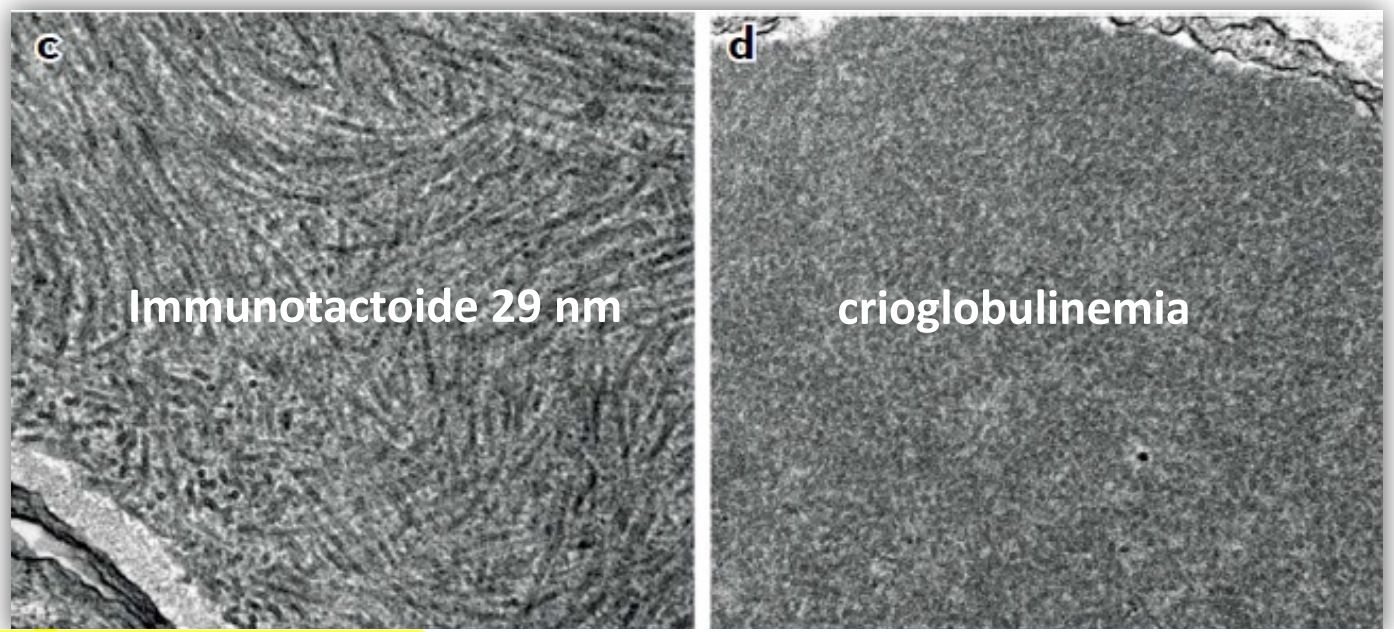
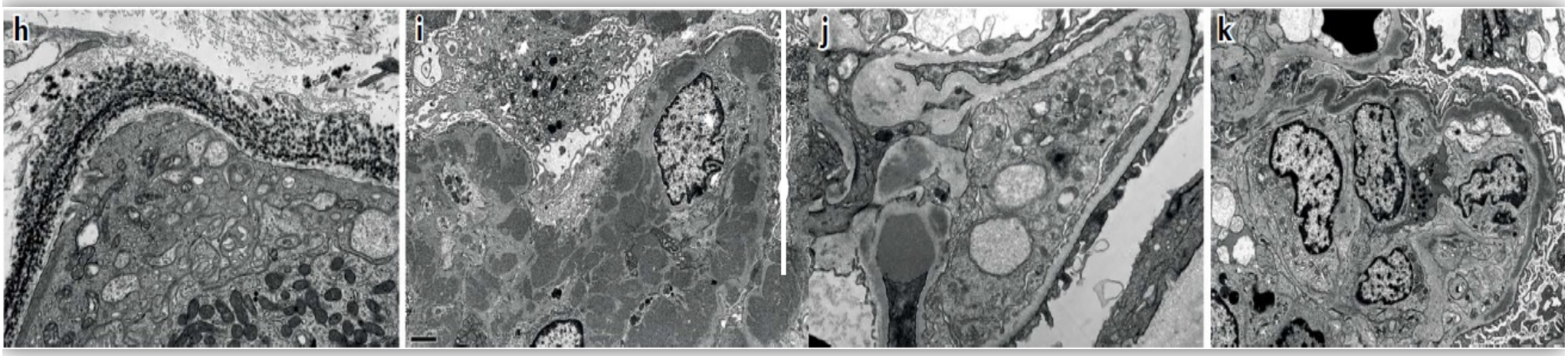


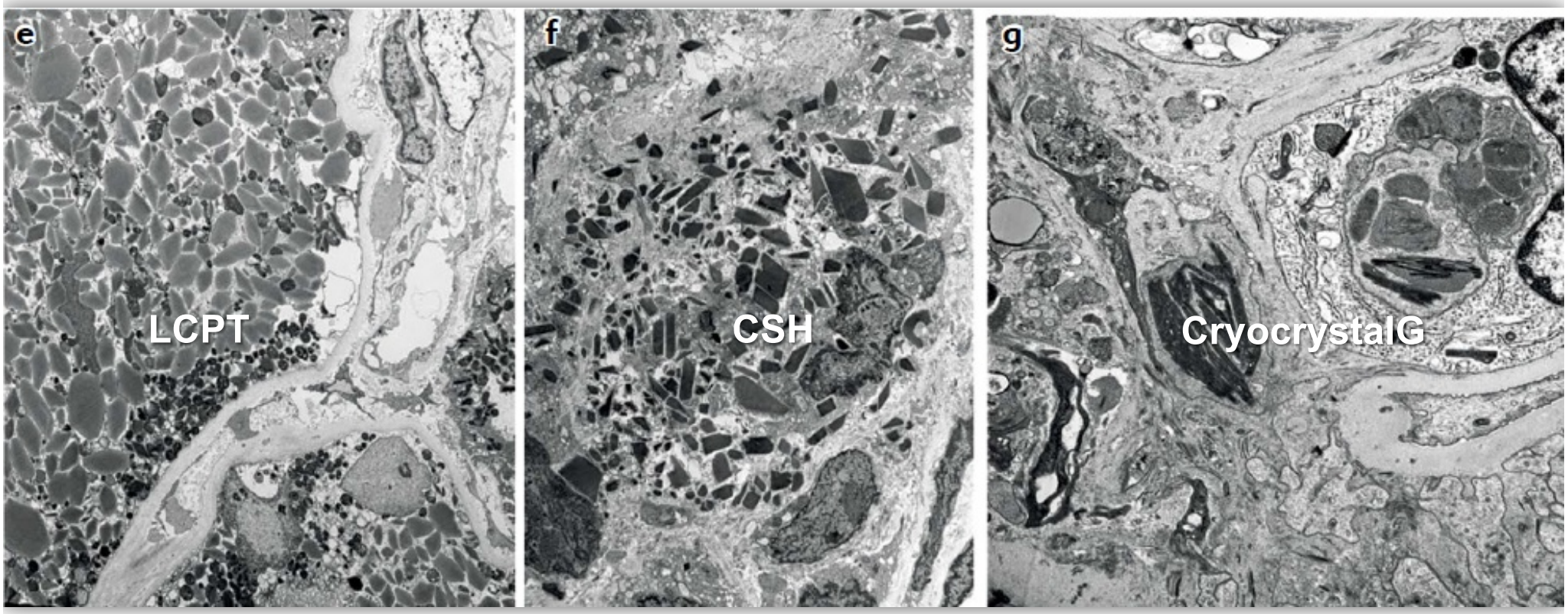
Fig. 3 | **Ultrastructural appearance of MGRS-associated lesions.** Top row: electron microscopy images showing fibrillar or microtubular deposits. **a** | Small randomly oriented fibrils of mean thickness 10 nm in a patient with immunoglobulin light-chain-κ amyloidosis (original magnification ×49,000). **b** | Randomly oriented fibrils with mean thickness of 15 nm in a patient with fibrillary glomerulonephritis (original magnification ×52,000).



c | Deposits composed of microtubules with hollow centres organized in parallel arrays and with a mean thickness of 26 nm in a patient with immunotactoid glomerulopathy (original magnification ×49,500). **d** | Focal deposits composed of short microtubules with hollow centres with a mean thickness of 29 nm in a patient with cryoglobulinaemic glomerulonephritis (original magnification ×40,000). Centre row: electron microscopy images showing crystals or inclusions.



h | Finely granular, highly electron-dense deposits along a tubular basement membrane in a patient with light-chain deposition disease (original magnification ×15,000). **i** | Large, discrete (mesangial, subendothelial and subepithelial) granular, electron-dense deposits in a patient with proliferative glomerulonephritis with monoclonal immunoglobulin deposits (original magnification ×6,000). **j** | Mesangial deposits and a hump-shaped subepithelial deposit located overlying the glomerular basement membrane reflection over the mesangium in a patient with C3 glomerulonephritis associated with monoclonal gammopathy (original magnification ×9,300). **k** | 'Sausage-like' thickening of the glomerular basement membrane associated with highly electron-dense intramembranous deposits in a patient with dense deposit disease associated with monoclonal gammopathy (original magnification ×4,800). MGRS, monoclonal gammopathy of renal significance.



e | Proximal tubular cells filled with moderately electron-dense, light-chain crystals that have rod and rhomboid shapes in a patient with crystalline light-chain proximal tubulopathy. The crystals are predominantly free within the cytoplasm, not membrane bound (original magnification ×2,700). **f** | Numerous light-chain crystals with rod, rectangle or rhomboid shapes within the cytoplasm of interstitial infiltrating histiocytes in a patient with crystal-storing histiocytosis (original magnification ×4,200). **g** | Needle-shaped, electron-dense crystals in the mesangium and within phagolysosomes of infiltrating inflammatory cells in a patient with cryocrystalglobulinaemia (original magnification ×9,300). The crystals showed monotypic staining for IgG and κ light chains on pronase immunofluorescence. Bottom row: electron microscopy images showing non-organized deposits.

Lesions classed as miscellaneous. The 'miscellaneous' subcategory of MGRS-associated lesions includes kidney diseases that are typically not associated with MGRS, such as anti-GBM disease secondary to a monoclonal gammopathy. The anti-GBM monoclonal antibody can be IgG or IgA[87–89]. In most patients with this disease, the anti-GBM antibody is not detectable in serum by commercially available enzyme-linked immunosorbent assay (ELISA) or multiplex flow immunoassays, which are designed to detect antibodies against only α3NC1. These patients experience frequent relapses and the disease recurs after kidney transplantation, which is not typical in patients with non-MGRS-associated anti-GBM disease[87–89]. A pattern of membranous nephropathy that is visually indistinguishable from that associated with polyclonal immunoglobulin-mediated membranous lesions on light microscopy and electron microscopy has been described in patients with monoclonal IgG deposits[90,91]. Although the phospholipase A2 receptor (PLA2R) was identified as the target of the monoclonal IgG in a single patient included in a small study, a larger study found that only 26% of patients showed evidence of antibodies to PLA2R and that none of those patients had a lymphoproliferative disorder[90,91]. Finally, Henoch–Schönlein purpura with IgA nephropathy has very occasionally been reported in patients with IgA monoclonal gammopathy or MM[92,93].

La biopsia renale nei pazienti affetti da MGRS

Utility of renal biopsy in the clinical management of renal disease

Neeraj Dhaun[1,2], Christopher O. Bellamy[3], Daniel C. Cattran[4] and David C. Kluth[2]

Although most nephrologists recognize several clear indications for a renal biopsy, it is still underutilized. It not only helps the clinician to manage the patient with CKD, but it can also help clarify the epidemiology of CKD, and aid research into the pathobiology of disease with the aim of discovering new therapies. It may be useful for instance in elderly patients with CKD, those with diabetes and presumed 'hypertensive nephropathy', and in some patients with advanced CKD as part of the pretransplant work-up. In some populations (for example, immunoglobulin A nephropathy and ANCA vasculitis), renal biopsy allows disease classification that may predict CKD progression and response to therapy.

Kidney International (2014) **85,** 1039–1048

Utility of renal biopsy in the clinical management of renal disease

Neeraj Dhaun[1,2], Christopher O. Bellamy[3], Daniel C. Cattran[4] and David C. Kluth[2]

"..... Renal biopsy is an essential procedure in the diagnosis of renal disease, and it is now hard to imagine that one could practice nephrology without knowing pathology. ....."

"..... However, there remain no consensus guidelines available to the global renal community outlining the indications for this important diagnostic and prognostic test. ....."

Kidney International (2014) **85,** 1039–1048

Utility of renal biopsy in the clinical management of renal disease

Neeraj Dhaun[1,2], Christopher O. Bellamy[3], Daniel C. Cattran[4] and David C. Kluth[2]

Table 1 | Standard indications for renal biopsy

Hematuria of presumed renal origin (absence of infection and urological investigations normal), usually in association with other factors such as significant proteinuria, hypertension, and presence of serum biomarkers (ANCA and dsDNA)
Significant proteinuria (>1 g/day)
Unexplained renal impairment
Renal involvement of systemic disease

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; dsDNA, double-stranded DNA.

Kidney International (2014) **85,** 1039–1048

Utility of renal biopsy in the clinical management of renal disease

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Table 2 | Suggested indications for renal biopsy in patients with diabetes with the appropriate clinical setting

Nephrotic-range proteinuria, but an absence of other diabetic microangiopathic complications (especially in type 1 diabetes[97])
Diabetes for an insufficient length of time for nephropathy to develop[40] (usually 10 years; this may include those with subnephrotic-range proteinuria and/or those with unexplained renal impairment)
Patients with minimal comorbidity in whom immunosuppressive treatment for an alternative diagnosis may be considered
Patients in whom a transplant may be considered and the natural history of their renal disease has been unusual for diabetic nephropathy

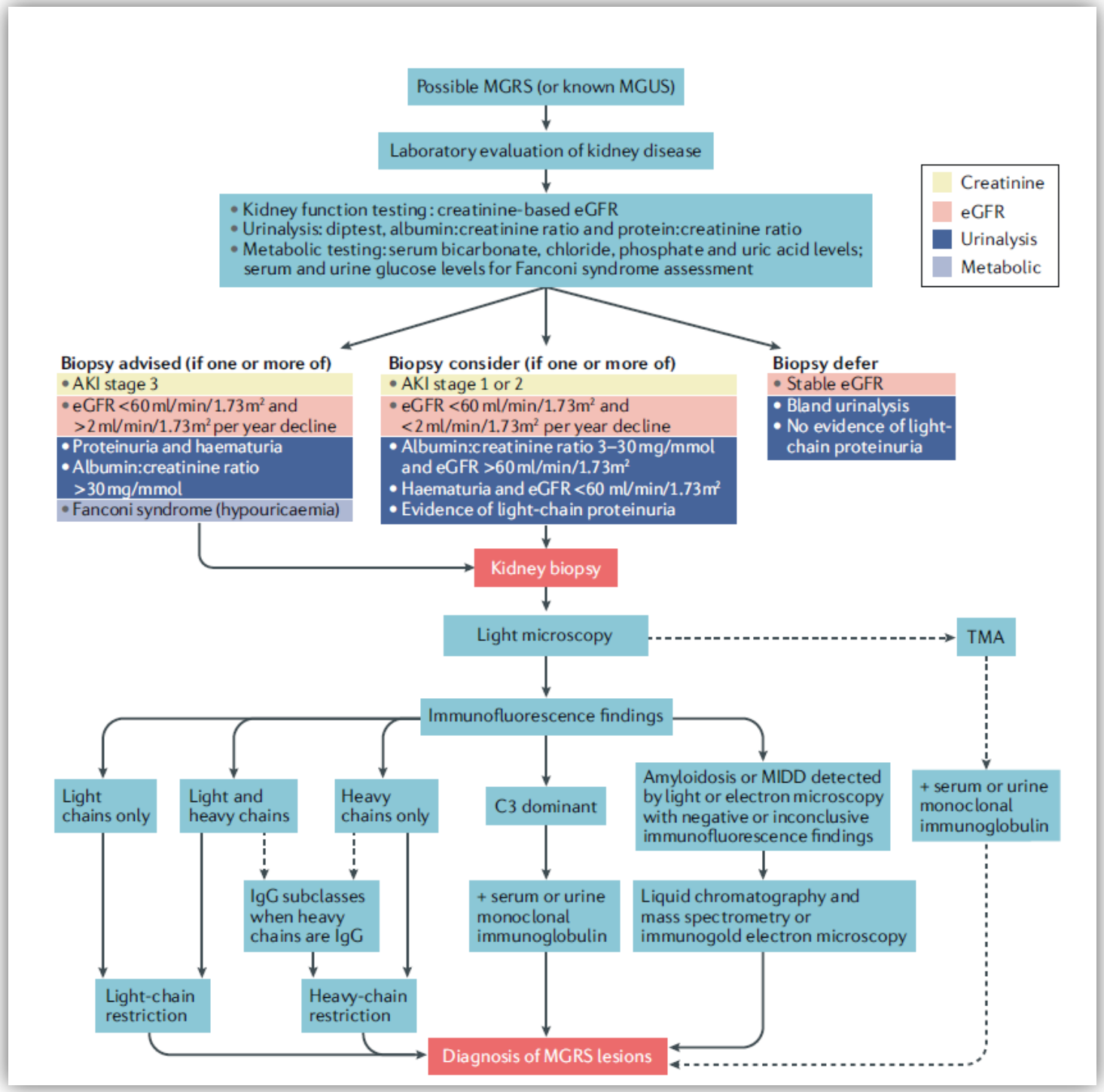
Microscopic hematuria of presumed renal origin *in isolation* is an insufficient indication for renal biopsy in patients with diabetes, and should be managed as in other patients—with renal biopsy indicated when it is associated with significant proteinuria or in the presence of other markers of disease, for example, seropositivity for anti-neutrophil cytoplasmic autoantibodies (ANCAs) or antibodies to double-stranded DNA (dsDNA).

Table 2 | **Consensus recommendations for the evaluation of MGRS-associated disorders**

Modality	Recommendations	Refs
Kidney biopsy	Recommended in the following patients: • Those with monoclonal gammopathy and unexplained kidney disease • Those with known risk factors for chronic kidney disease but an atypical clinical course • Patients with kidney disease and monoclonal gammopathy aged <50 years	NA

Summary

MGRS is a new classification of pathogenic clonal proliferative disorders that produce a nephrotoxic protein. The term MGRS was needed to improve the classification of these diseases for research purposes, and to accurately categorize them as pathological, so that government agencies could allocate the resources necessary for their treatment. The diagnosis of MGRS can be established only by performing a kidney biopsy that either demonstrates the presence of monotypic immunoglobulin deposits or infers their involvement in the case of C3 glomerulonephritis or thrombotic microangiopathy with a circulating monoclonal immunoglobulin. Clinicians will need to balance the risk of missing a diagnosis against those of the complications of renal biopsy; therefore, the judicious use of renal biopsy is important. Detection of a monoclonal immunoglobu-


Possible MGRS (or known MGUS)
Laboratory evaluation of kidney disease
• Kidney function testing: creatinine-based eGFR
• Urinalysis: diptest, albumin:creatinine ratio and protein:creatinine ratio
• Metabolic testing: serum bicarbonate, chloride, phosphate and uric acid levels; serum and urine glucose levels for Fanconi syndrome assessment
Creatinine
eGFR
Urinalysis
Metabolic
Biopsy advised (if one or more of)
• AKI stage 3
• eGFR <60 ml/min/1.73m² and >2 ml/min/1.73m² per year decline
• Proteinuria and haematuria
• Albumin:creatinine ratio >30 mg/mmol
• Fanconi syndrome (hypouricaemia)
Biopsy consider (if one or more of)
• AKI stage 1 or 2
• eGFR <60 ml/min/1.73m² and <2 ml/min/1.73m² per year decline
• Albumin:creatinine ratio 3–30 mg/mmol and eGFR >60 ml/min/1.73m²
• Haematuria and eGFR <60 ml/min/1.73m²
• Evidence of light-chain proteinuria
Biopsy defer
• Stable eGFR
• Bland urinalysis
• No evidence of light-chain proteinuria
Kidney biopsy
Light microscopy
TMA
Immunofluorescence findings
Light chains only
Light and heavy chains
Heavy chains only
C3 dominant
Amyloidosis or MIDD detected by light or electron microscopy with negative or inconclusive immunofluorescence findings
+ serum or urine monoclonal immunoglobulin
IgG subclasses when heavy chains are IgG
+ serum or urine monoclonal immunoglobulin
Liquid chromatography and mass spectrometry or immunogold electron microscopy
Light-chain restriction
Heavy-chain restriction
Diagnosis of MGRS lesions

The Incidence of Major Hemorrhagic Complications After Renal Biopsies in Patients with Monoclonal Gammopathies

Richard Fish,* Jennifer Pinney,† Poorva Jain,‡ Clara Addison,§ Chris Jones,* Satish Jayawardene,* John Booth,† Alexander J. Howie,‖ Tareck Ghonemy,§ Shahista Rajabali,§ David Roberts,§ Lucy White,§ Sofia Khan,§ Matthew Morgan,§¶ Paul Cockwell,§¶ and Colin A. Hutchison§¶

Background and objectives: Monoclonal gammopathies frequently cause renal disease, but they may be an incidental finding. Assessment of renal pathology in the context of renal dysfunction and a monoclonal gammopathy therefore serves as a useful diagnostic tool and, in addition, provides prognostic information. There is, however, a theoretical risk of increased hemorrhagic complications from renal biopsies in this setting. The purpose of this study was to determine the incidence of significant hemorrhagic complications after renal biopsies in patients with monoclonal gammopathies.

Conclusions

This study showed that the risk of a major hemorrhagic complication in patients with a monoclonal gammopathy after a percutaneous renal biopsy is not increased. We suggest that the assessment of renal histology in patients with monoclonal gammopathies remains a valuable diagnostic tool to guide management and help predict clinical outcomes for these.

Intraglomerular crystal deposition	0.7 (1)	0
ATN	2.7 (4)	0
Other renal findings[b]	6.8 (10)	0

ATN, acute tubular necrosis; LCDD, light chain deposition disease

[a]Two of the six bleeding complications in patients with cast nephropathy were hematomas. One of these required radiologic intervention. The remaining four complications were significant hematuria and did not require radiologic intervention.

[b]Other renal findings included diabetic nephropathy; hypertensive damage; end-stage kidney; membranous nephropathy; and focal segmental glomerular sclerosis.

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CLINICA

Table 2 | Main clinical, pathological, and immunological characteristics of glomerular disorders with organized Ig deposits in MGRS

Glomerular disease	Renal symptoms	Extra-renal involvement
AL amyloidosis *AH amyloidosis* *AHL amyloidosis*	Proteinuria, NS CKD Hypertension and hematuria uncommon	Frequent: heart, liver, peripheral nerve
ITGN/GOMMID	Proteinuria, NS CKD Microhematuria Hypertension	Uncommon (peripheral nerve, skin)
Type I cryoglobulinemic GN	Proteinuria, NS CKD Microhematuria Hypertension Possible nephritic syndrome, AKI, anuria	Frequent: skin, peripheral nerve, joints

Table 3 | Main clinical, pathologic

Glomerular disease	Renal symptoms	non-organized Ig de Extrarenal involvement
MIDD	Proteinuria, NS CKD Microhematuria Hypertension	Common, often asymptomatic: heart, liver, lung
PGNMID	Proteinuria, NS CKD Microhematuria Hypertension	None
C3 glomerulopathy with monoclonal gammopathy	Proteinuria, NS CKD Microhematuria Hypertension	None

Diagnosis of monoclonal gammopathy of renal significance

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Table 1 | Main clinical, pathological, and immunological characteristics of tubular disorders in MGRS

Tubular disorder	Renal symptoms	Light microscopic findings	IF findings (Ig type)	Ultrastructural findings	Extrarenal involvement	Hematological disease
Light chain Fanconi syndrome	Proximal tubule dysfunction[a] Slowly progressive CKD	PTC atrophy and dedifferentiation Intra-cytoplasmic inclusions	PTC LC inclusions Almost always kappa: Vκ1, or Vκ3 (rare)	Crystals (rhomboid) within PTC lysosomes or free in the cytoplasm	Bone (osteomalacia)	MGRS Symptomatic MM and WM uncommon
Proximal tubulopathy without crystals	Tubular proteinuria ± progressive CKD	PTC atrophy and dedifferentiation PTC cytoplasmic swelling	PTC LC staining Lambda or kappa	Amorphous granular accumulations of LCs Increased lysosomes with a mottled appearance	None	MGRS MM
Crystal-storing histiocytosis	Proximal tubule dysfunction CKD	Histiocytes with crystalline inclusions (pseudo-pseudo Gaucher cells) in the interstitium and perirenal fat PTC atrophy and dedifferentiation	PTC LC inclusions Mostly kappa :Vκ1 or Vκ3	Crystals (needle-shaped) within histiocytes and occasionally in PTC and glomerular cells	Bone marrow, liver, spleen, LN, lung, skin, cornea	MGRS MM LPL

Abbreviations: CKD, chronic kidney disease; IF, immunofluorescence; LC, immunoglobulin light chains; LN, lymph nodes; LPL, lymphoplasmacytic lymphoma; MGRS, monoclonal gammopathy of renal significance; MM, multiple myeloma; PTC, proximal tubular cells; WM, Waldenström's macroglobulinemia.
[a]Most common symptoms: hypouricemia, hypophosphatemia, normoglycemic glycosuria, generalized aminoaciduria, low-molecular weight proteinuria, and proximal (type 2) renal tubular acidosis.

Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits is associated with high rate of early recurrence in the allograft

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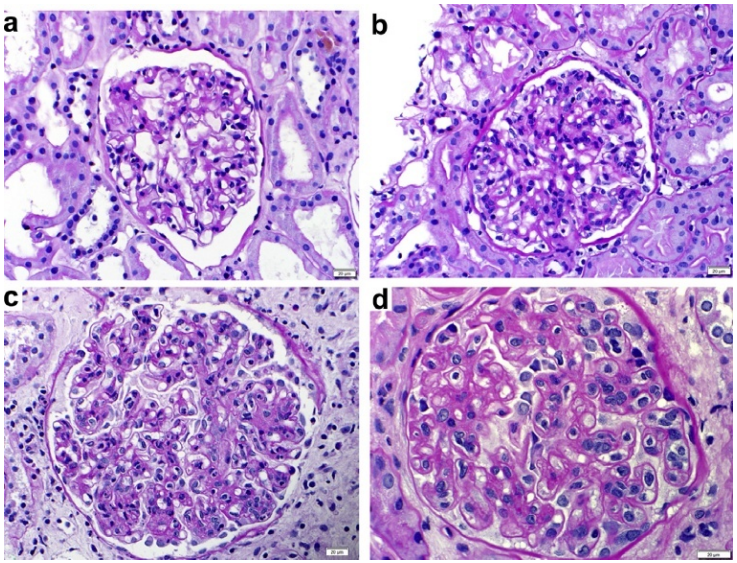
In summary, PGNMID has a very high recurrence rate in renal allografts. Most cases recur early post-Tx, and detection is greatly enhanced by use of protocol allograft biopsies. Clinical behavior and histology of allograft PGNMID are variable. Most cases respond to immunosuppressive therapy, although disease relapse is frequent. Prognosis is guarded, with a median allograft survival of 92 months.



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TERAPIA

Bridging the Divide: An Onco-Nephrologic Approach to the Monoclonal Gammopathies of Renal Significance

Table 2. Therapeutic options for monoclonal gammopathies of renal significance

Agent (Dosage Form)	Clone Sensitivity		Dose Adjustment for eGFR?	Described Kidney-Associated Toxicities	Common Adverse Events
	B Cell	Plasma Cell			
Proteasome inhibitors					
Bortezomib (IV, SC)	X	X	No	None	Thrombocytopenia Peripheral neuropathy Varicella zoster reactivation
Carfilzomib (IV)	X	X	Yes	AKI, thrombotic microangiopathy	Thrombocytopenia Dyspnea Hypersensitivity reaction Varicella zoster reactivation
Monoclonal antibodies					
Rituximab (anti-CD20) (IV)	X		No	None	Infusion reactions Hepatitis B reactivation
Daratumumab (anti-CD38) (IV)		X	No	None	Infusion reactions
Cytotoxic agents					
Cyclophosphamide (IV, PO)	X	X	No	None	Nausea Cytopenias
Melphalan (IV, PO)	X	X	Yes	None	Nausea Cytopenias
Bendamustine (IV)	X	X	Yes	None	Cytopenias
Immunomodulatory agents					
Thalidomide (IV, PO)	X	X	No	Hyperkalemia observed in renal insufficiency	Constipation Fatigue, somnolence Peripheral neuropathy Venous thrombosis Rash Teratogenicity
Lenalidomide (IV)	X	X	Yes	Increased myelosuppression in renal insufficiency, AKI observed in AL amyloidosis	Cytopenias Venous thrombosis Diarrhea Constipation Rash Teratogenicity
Pomalidomide (IV)		X	Unknown	No	Cytopenias Venous thrombosis Diarrhea; Constipation Teratogenicity

Bridging the Divide: An Onco-Nephrologic Approach to the Monoclonal Gammopathies of Renal Significance

Table 2. (Continued)

Agent (Dosage Form)	Clone Sensitivity		Dose Adjustment for eGFR?	Described Kidney-Associated Toxicities	Common Adverse Events
	B Cell	Plasma Cell			
Other agents					
Fludarabine (IV)	X		Yes	None	Cytopenias Opportunistic infections Hemolytic anemia Secondary myeloid neoplasms
Pentostatin (IV)	X		Yes	Increased creatinine	Cytopenias Opportunistic infections Hemolytic anemia
Ibrutinib (PO)	X		Unknown	Increased creatinine	Bleeding Tachyarrhythmias

IV, intravenous; SC, subcutaneous; PO, oral; AL, amyloid light chain amyloidosis.

Table 6 – Therapeutic regimens proposed for MGRSs.

Disease	Treatment
Proliferative glomerulonephritis with monoclonal Ig deposits	• Stage 1–2 CKD, proteinuria <1 g/day: observation • Stage 1–2 CKD with proteinuria >1 g/day, progressive CKD or stage 3–4 CKD: - Cyclophosphamide + bortezomib + dexamethasone if IgG or IgA - Rituximab ± cyclophosphamide + dexamethasone if IgM - If <65 years: high-dose melphalan following an HSCT • Stage 5 CKD candidate for kidney transplant: high-dose melphalan + HSCT
Type 1 cryoglobulinaemia-associated glomerulonephritis	• Paucisymptomatic or low-grade B-cell proliferation: observation • Symptomatic: - Plasmacytic clone: bortezomib + cyclophosphamide ± thalidomide - Lymphoplasmacytic clone: rituximab - Alternative: bendamustine
Immunotactoid glomerulopathy	• Treatment regimens similar to those employed in CLL, based on cyclophosphamide or bendamustine ± rituximab • For isolated gammopathy, treatment regimen based on bortezomib
Ig-related amyloidosis (AL, AH, AHL)	• Classification in three stages according to the increase in levels of NT-proBNP and troponin • Stage 1–2: melphalan or cyclophosphamide + dexamethasone + bortezomib • Stage 3: cyclophosphamide + dexamethasone + bortezomib • Heart transplant if cardiac involvement; HSCT in selected cases
Monoclonal Ig deposition disease	• Stage 1–3 CKD: cyclophosphamide + bortezomib + dexamethasone, with subsequent HSCT in selected cases. Alternative: bendamustine • Stages 4–5 CKD: cyclophosphamide + bortezomib + dexamethasone + HSCT if candidate for kidney transplant
Light chain proximal tubulopathy	• Stage 1–3 CKD: cyclophosphamide, bortezomib or thalidomide + HSCT in selected cases • Stage 4–5 CKD: HSCT if they are candidates for a kidney transplant. If not, conservative management

AH: heavy-chain amyloidosis; AHL: heavy- and light-chain amyloidosis; AL: light-chain amyloidosis; CKD: chronic kidney disease; HSCT: haematopoietic stem cell transplantation; Ig: immunoglobulin; NT-proBNP: N-terminal pro-brain natriuretic peptide.
Source: Adapted from original by Fermand et al.[107]

Caso clinico

Tipizzazione linfocitaria: 30% dei linfociti periferici presenta fenotipo CD5+, CD10-, CD23+,CD43+, FMC7+,CD200+, SmIg con restrizione clonale per le catene leggere kappa. Quadro compatibile con malattia linfoproliferativa a cellule B CD5+ (B-CLL/leucemia prolinfocitica).

BOM midollo comprendente componente plasmacellulare che costituisce meno del 10% della cellularità totale senza restrizione monotipica per le catene leggere.

Comparsa di neuropatia sensitiva severa arti inferiori.

Test di Shirmer positivo, Xerostomia.

Ecografia collo: ghiandole salivari nella norma. Noduli tiroidei. Non LN

V ematologica e reumatologica: vasculite crioglobulinemica nell'ambito di S. di Sjogren. GNMP, neuropatia sensitiva di grado marcato. Porpora regredita con gli steroidi (MP 750 mg x 3 gg e poi pred 0.5/mg/kg). Somministrato quindi RTX 1 g ogni 15 gg per 2 volte.

Diagnosi di dimissione

Sindrome nefritica acuta da GNMP in corso di vasculite crioglobulinemia, sindrome di Sjogren

Referto ME

Due glomeruli, lumi spesso occlusi da cellule infiammatorie mononucleate, MBG nella norma, mesangio espanso sia nella componente cellulare che stromale e associato ad alcuni depositi. Pedicelli fusi per lunghi tratti e ipertrofia dei podociti.

Conclusioni: quadro ME compatibile con GNMP