
Immune Complex Disease in Cancer: Future of Antigens

Paraneoplastic glomerulonephritis and the search for the antigen

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Disclosures

None

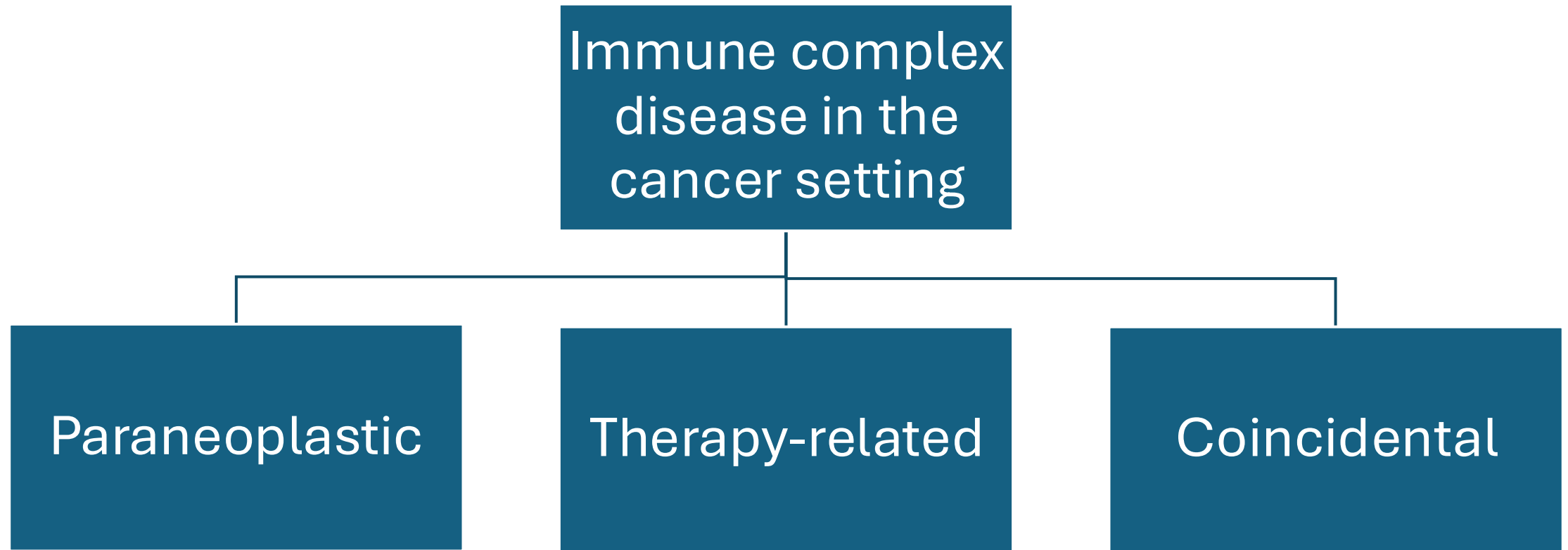
Objectives

- 01 Paraneoplastic glomerulonephritis - which glomerular lesions accompany malignancy, and what makes this association credible?
- 02 Membranous nephropathy and the antigen-based classification
- 03 The story with other paraneoplastic immune complex-mediated GNs, and what comes next
- 04 The pathologist's approach to diagnosis – past, present, and future

WHERE WE SIT

Membranous nephropathy made the antigen visible; IgA nephropathy and “lupus-like” GN suggest this may not generalize

Immune Complex Disease in Cancer



Paraneoplastic Glomerulonephritis: The Landscape

Recognized since
the 1920s

Solid tumors

Hodgkin
lymphoma

CLL / NHL

Other

Membranous nephropathy

Solid tumors; lung and GI
cancers predominate.

Minimal change disease

Hodgkin lymphoma is the
classic association.

MPGN

CLL/NHL and other
lymphoproliferative
disorders.

Also reported

IgAN, FSGS, crescentic
GN, TMA, AA amyloidosis.

CLINICAL CONTEXT

GN may precede the cancer diagnosis and mimic “idiopathic” disease → maintain a high index of suspicion

The Unifying Mechanisms: Immune Complexes

1

Tumor antigen → antibody → immune complex

A tumor-derived product becomes the target of a humoral response.

2

Molecular mimicry

Tumor antigen cross-reacts with a podocyte or other self antigen.

3

Tumor-driven immune dysregulation

Loss of tolerance, altered cytokine milieu, or polyclonal B-cell activation drives immune complex formation.

SIGNATURE OF A TRUE PARANEOPLASTIC LINK

Close temporal proximity | Remission with tumor treatment | Recurrence with tumor relapse | Exclusion of primary disease

Membranous Nephropathy: A Paradigm Shift

OLD DICHOTOMY

Primary $\approx 70\%$ | Secondary $\approx 30\%$
Useful clinically, but biologically coarse.

2009

PLA2R explains majority of primary MN.

2014 → NOW

THSD7A + a rapidly expanding antigen spectrum.

Laser-capture microdissection + mass spectrometry opened an antigen void.

PLA2R

THSD7A

EXT1/2

NELL1

SEMA3B

NCAM1

PCDH7

CNTN1

HTRA1

FAT1

NTNG1

PCSK6

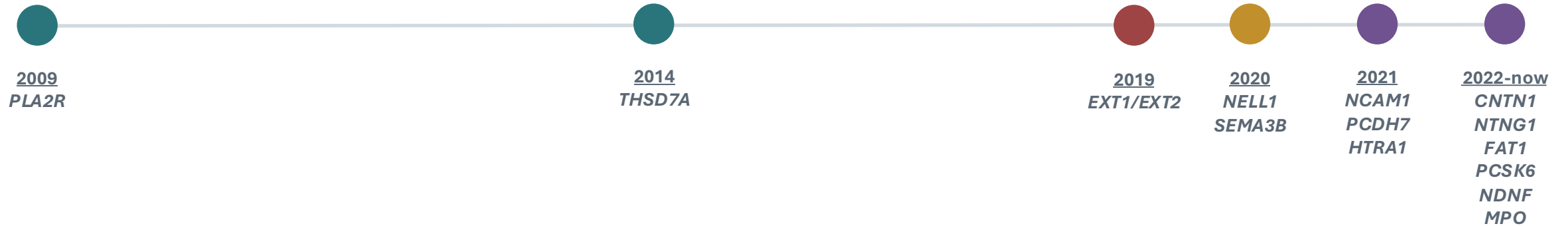
NDNF

MPO

TAKEAWAY

10-15 antigens now explain $\sim 80-90\%$ of MN, each with distinct associations, IgG subclasses, and prognosis

The Antigenic Spectrum of Membranous Nephropathy



TRANSMEMBRANE

PLA2R • THSD7A • NCAM1 • PCDH7 • FAT1 • CNTN1

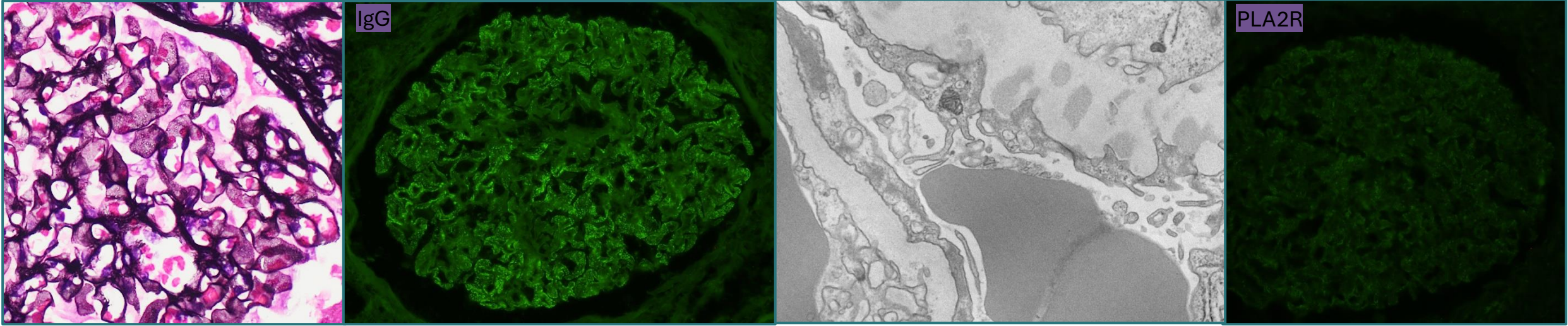
SECRETED

NELL1 • SEMA3B • NDNF • PCSK6

ANTIGENIC EXPLOSION

Numerous antigens being found, with variable prevalence, and outpacing development of concurrent serologic testing

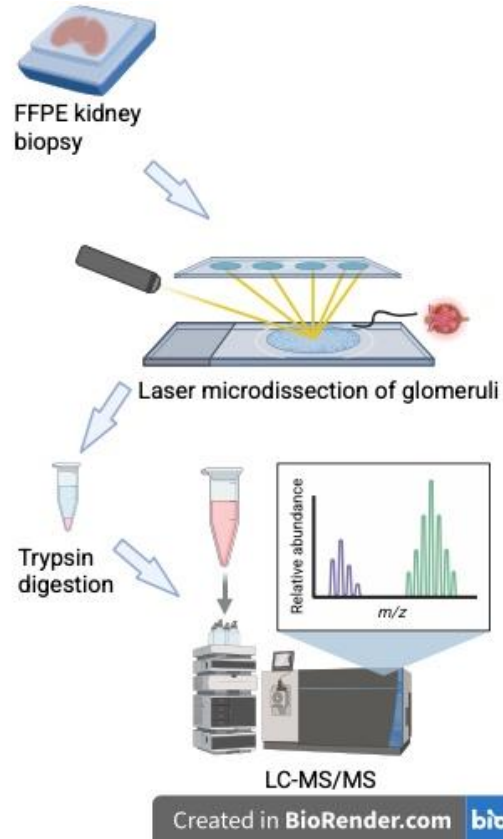
Clues on Biopsy



SUBTLE DIFFERENCES MAY SUGGEST THE UNDERLYING ANTIGEN

Variations in IgG subclass dominance | Presence/Absence of mesangial deposits | Tubuloreticular inclusions | Segmental deposits

Laser Microdissection + Mass Spectrometry



WRINKLES

Data-dependent acquisition → fragmentation and spectral analysis is performed only on peptide signals that rise above the noise in a full-scan spectrum

- Morelle, et al. (2025) used data-independent acquisition – evaluating all peptides within a defined mass-to-charge window, potentially resulting in a more in-depth identification – increased antigen detection rate in PLA2R(-) MN from **46%** → **83%**

Immunofluorescence v/s mass spectrometry

- Zand, et al. (2025) reports that **~3%** of PLA2R(-) MN by immunofluorescence is reclassified as PLA2R(+) by mass spectrometry

WHY IT WORKS

Antigens accumulate in massive subepithelial deposits in MN, resulting in high signal-to-noise ratio as compared to controls

THSD7A: Proof-of-Concept for a Shared Tumor-Kidney Antigen

MALIGNANCY SIGNAL

~16% in a large series (31/195); across cohorts, malignancy is reported in ~6-25% (lung, GI, prostate, breast).

BIOLOGY

IgG4-predominant; podocyte antigen can also be ectopically expressed by tumor tissue.

CLINICAL PROOF

Gallbladder carcinoma expressed THSD7A; antibody titers and proteinuria fell after tumor treatment

CORRESPONDENCE



A Mechanism for Cancer-Associated Membranous Nephropathy

Published May 19, 2016 | N Engl J Med 2016;374:1995-1996 | DOI: 10.1056/NEJMc1511702 | VOL. 374 NO. 20

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SHARED ANTIGEN/MOLECULAR MIMICRY

THSD7A appears to be a malignancy-enriched antigen, but the association is not absolute

NELL1: Malignancy-Enriched Antigen

MALIGNANCY

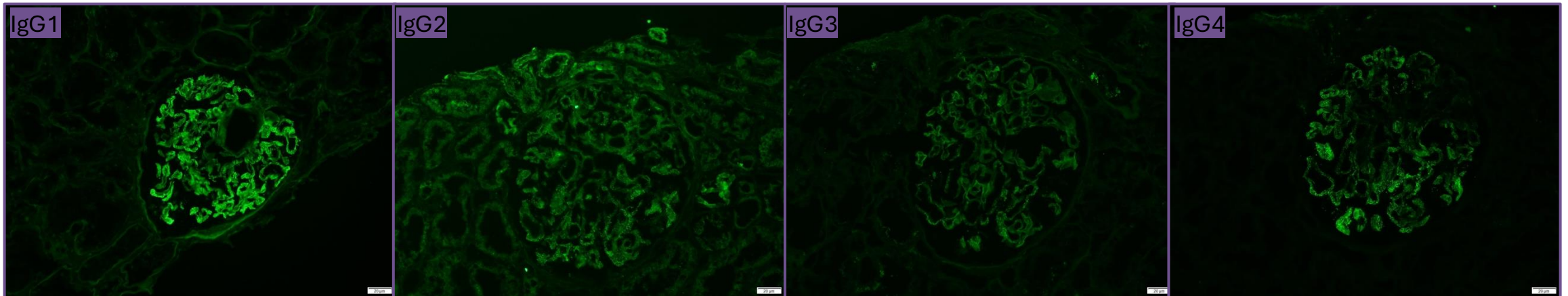
~10-30% across series; 33% concurrent malignancy in the original Caza cohort

PATHOLOGY

Secreted; second most common MN antigen; frequently with distinctive segmental pattern; IgG1-dominance

CAUTION

Also linked to drugs/exposures, and NELL1 positivity does not equate to underlying cancer; substantial geographic variability



SHARED ANTIGEN/MOLECULAR MIMICRY

Case reports of concurrent NELL1-positive staining in colon cancer and esophageal carcinoma

MN on Pathology: Raising the Possibility of Malignancy

>8 INFLAMMATORY CELLS / GLOMERULUS

Specificity ~75%, sensitivity ~92% in the Lefaucheur (2006) cohort, but it is not an absolute rule.

IgG SUBCLASS SHIFT

Cancer-associated MN more often shows IgG1/IgG2 dominance; primary MN classically IgG4.

DEPOSIT DISTRIBUTION

Presence of subendothelial and/or mesangial deposits can suggest "secondary" MN, including malignancy-associated MN.

PROLIFERATIVE / INFLAMMATORY CLUES

Endocapillary hypercellularity, mesangial hypercellularity, and leukocyte infiltration are useful "secondary MN" clues.

PATHOLOGY REPORTING

If MN is PLA2R(-), IgG1 or IgG2 predominant, or has subendothelial/mesangial involvement -> flag the possibility of malignancy

Why the MN Antigen Model May Not Transfer Cleanly

- 1 Membranous Nephropathy**

A discrete podocyte-expressed protein sits inside a clean, high-abundance subepithelial deposits, making it findable by mass spectrometry
- 2 IgA Nephropathy**

The target is a Gd-IgA1 glycoform within a multi-hit immune complex pathway, not a novel protein
- 3 “Lupus-like” Glomerulonephritis**

Full-house polyclonal immune complex disease with no single defined target

SPOILER

These paraneoplastic GNs can be indistinguishable from “idiopathic” GNs, thus require high index of suspicion and clinical correlation

“Paraneoplastic” IgA Nephropathy

1

Gd-IgA1

Galactose-deficient
IgA1

2

Autoantibody

Anti-glycan antibody
(IgG and IgA)

3

Immune complex

Circulating immune
complex

4

Kidney

Mesangial deposition

WHAT IS THE “ANTIGEN”?

Exposed GalNAc hinge region – a post-translational neo-epitope, not a tumor-specific; newer findings (IgA-MESCA; anti-CBX3) don’t distinguish as tumor.

WHY CANCER MAY MATTER

Mucosal immune dysregulation may be amplified by transformed cells, altered glycosylation, or cross-reactivity.

REPORTED TUMOR CONTEXT

Buccal/oropharyngeal | Nasopharyngeal | Respiratory/lung | Renal cell carcinoma | Lymphoma

“Lupus-like” Glomerulonephritis: A Pattern, Not an Antigen

“Full-house” IF pattern

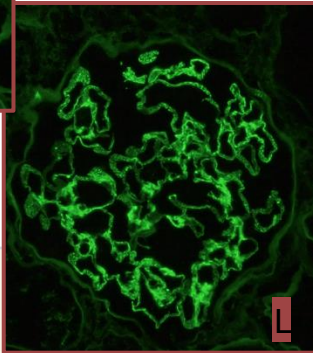
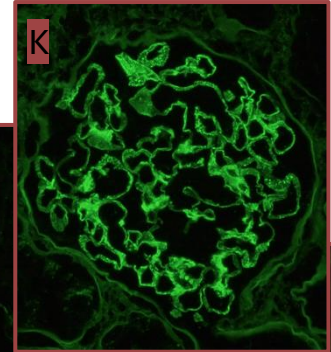
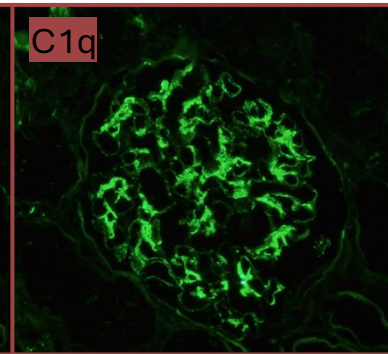
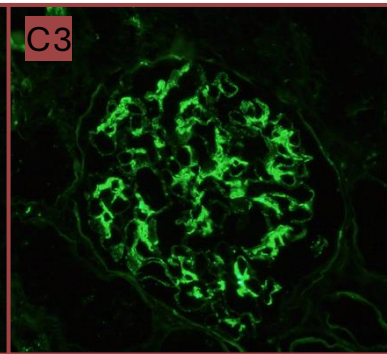
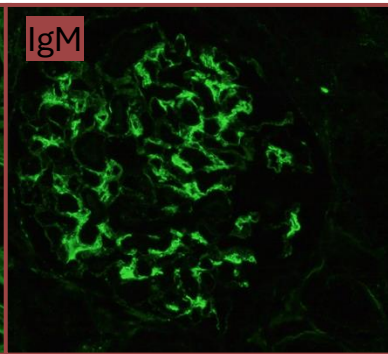
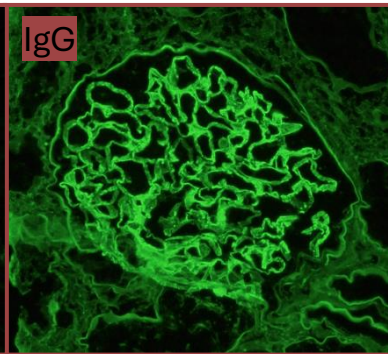
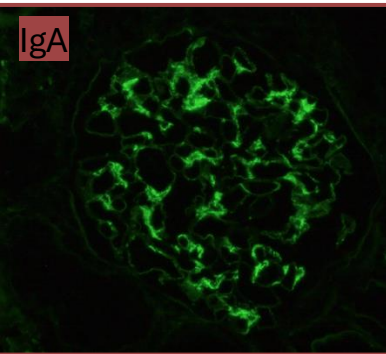
IgA

IgG

IgM

C3

C1q



WHEN IT APPEARS

Lymphoproliferative disorders, MALT lymphoma, mantle cell lymphoma, trophoblastic and solid tumors.

WHAT WE SEE

Polyclonal autoantibodies → diverse immune complexes → mesangial/subendothelial injury.

WHAT WE DON'T KNOW

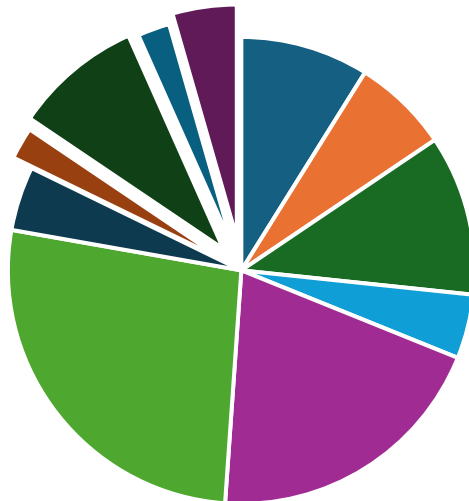
Inciting antigen undefined.

IMPORTANT SEPARATION

Membranous lupus-associated antigens (EXT1/EXT2; NCAM1) are autoimmune-associated, NOT established as cancer-associated

Throwing in a Caveat: Immune Checkpoint Inhibitors

Glomerular Diseases



■ AA Amyloid	■ Anti-GBM	■ C3GN	■ FSGS
■ MCD	■ Pauci-immune	■ TMA	■ MN
■ IgAN	■ Lupus-Like	■ ICGN	

[Distribution among 45 biopsy confirmed ICI-associated *glomerular* cases; AIN (the dominant ICI kidney lesion) is not shown here]

WRINKLES

Immune complex-mediated GN is increasingly reported with ICI therapy - IgA nephropathy, “Lupus-like” nephritis, membranous nephropathy have all been reported

- However, context matters:
 - AIN is present in ~80-90% of ICI kidney biopsies
 - Glomerular disease in the minority
- Kitchlu et al’s systematic review (2021) found only 45 biopsy-confirmed ICI-associated glomerular cases (through 02/2020); 41% with concomitant AIN
 - Within those, pauci-immune GN/renal vasculitis, podocytopathies, and C3GN were the most frequent lesions; immune complex-mediated disease was a small fraction (8/45)

HYPOTHESES

Breaking tolerance | Unmasking cryptic antigens | Epitope spreading | Generating neoantigens

Why MN Antigens are Findable While IgAN/“Lupus-like” Aren’t

	MN	IgAN	“Lupus-like” GN
Target	Dominant protein antigen	Gd-IgA1 glycoform	Polyclonal / multiple
Deposit	Subepithelial	Mesangial	Mesangial + subendothelial
Capture	LCM/MS + IHC	Glycomic + antibody profiling	Immune complex / repertoire
Antigenic approach	One antigen	Multi-hit pathway	Network of targets / clones

CONSEQUENCE

Antigen-based reclassification is realistic (and here?) for MN; the others may need alternative approaches

The Future

MN

Broader serology beyond PLA2R/THSD7A; NELL1 assays exist (currently in research form); detecting dual-antigen disease.

IgAN

Characterize glycan signatures, anti-glycan antibodies, and the circulating immune-complex repertoire.

Lupus-like GN

Profile autoantibody specificity, immune complex composition, clonal B-cell responses.

Across all three

Pair kidney + tumor + serum + immune repertoire longitudinally.

SHIFTING PATHOLOGY SIGN-OUT

“(Primary/Secondary) Membranous nephropathy” → “Membranous nephropathy, NELL1-associated”

Practical Implications

NEPHROLOGISTS

- Improved cancer stratification
- Targeted screening
- Clinical remission with treatment of cancer

ONCOLOGISTS

- Further recognition of paraneoplastic (and therapy-associated) kidney diseases
- Monitoring treatment responses and recurrence

PATHOLOGISTS

- Expanded antigen testing panels and protocols
- Accessibility

PATIENTS

- More precise diagnoses
- Less empiric therapy
- Increased cancer screening?

KEY POINT

Precision rises as antigens are defined, but requires close coordination among pathology, nephrology, and oncology.

Take-Home Messages

- 01 Paraneoplastic GN reflects immune complex-mediated disease; membranous nephropathy is the prototype and the antigen success story
 - 02 THSD7A and NELL1 refine cancer-associated MN, but antigen positivity is only a probabilistic malignancy flag
 - 03 IgAN centers on a Gd-IgA1 glycan neo-epitope and a four-hit pathway, not a single tumor protein
 - 04 Lupus-like GN is a full-house, polyclonal process with undefined inciting antigen
 - 05 Pathology discriminators and antigenic positivity are probability modifiers and not stand-alone cancer diagnostic findings; pattern recognition is essential, but incomplete
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