ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
Ο ΕΥΑΓΓΕΛΙΣΜΟΣ

Δώμα Ευγγελισμού,
23.10.19

«Γυναίκα ασθενής 37 ετών με ψωρίαση και οξεία νεφρική βλάβη»

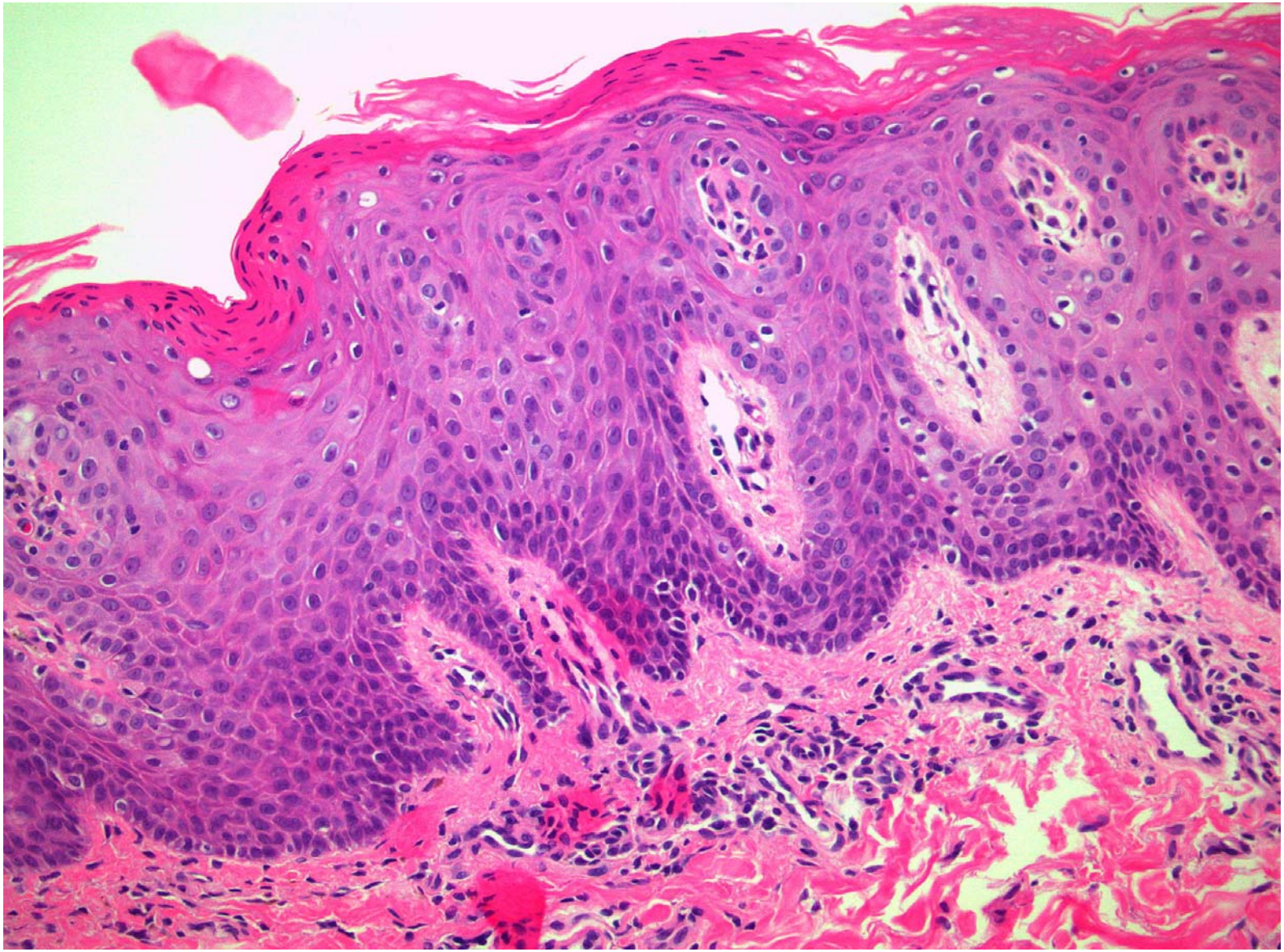
Σταύρος Παντελάκος, Ειδικευόμενος Ιατρός
Χριστίνα Βουρλάκου, Διευθύντρια
Γ.Ν.Α. «Ο Ευαγγελισμός», Παθολογοανατομικό τμήμα
Συντονίστρια Διευθύντρια Δ. Ροντογιάννη

ΒΙΟΨΙΑ ΔΕΡΜΑΤΟΣ

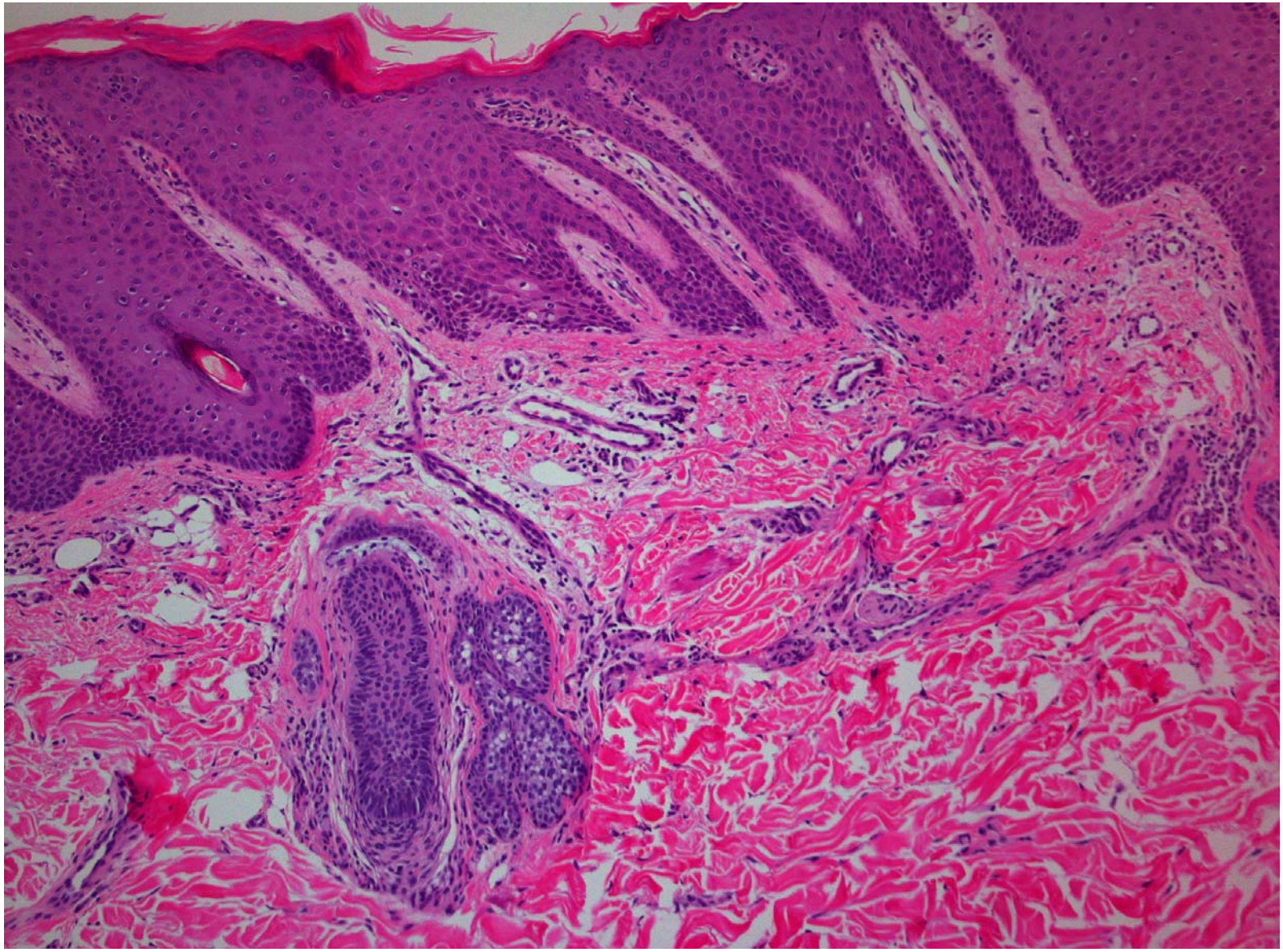
Ευρήματα συμβατά ψωρίασης [psoriasis] σύμφωνα και με το αναφερόμενο ιστορικό.

Σχόλια: **1.** Από ιστολογική άποψη η ψωρίαση είναι μια δυναμική δερματοπάθεια που αλλάζει κατά τη διάρκεια της εξέλιξης της κάθε βλάβης. Κατατάσσεται σε πρώιμο στάδιο, σε προχωρημένο στάδιο, και απώτερες βλάβες. Οι βλάβες είναι συνήθως διαγνωστικές στα πρώτα στάδια ή κοντά στην περιφέρεια των προχωρημένων πλακών. Τα Munro microabscesses και Kogoj micropustules είναι διαγνωστικές ενδείξεις της ψωρίασης, αλλά δεν είναι πάντα παρόντα.

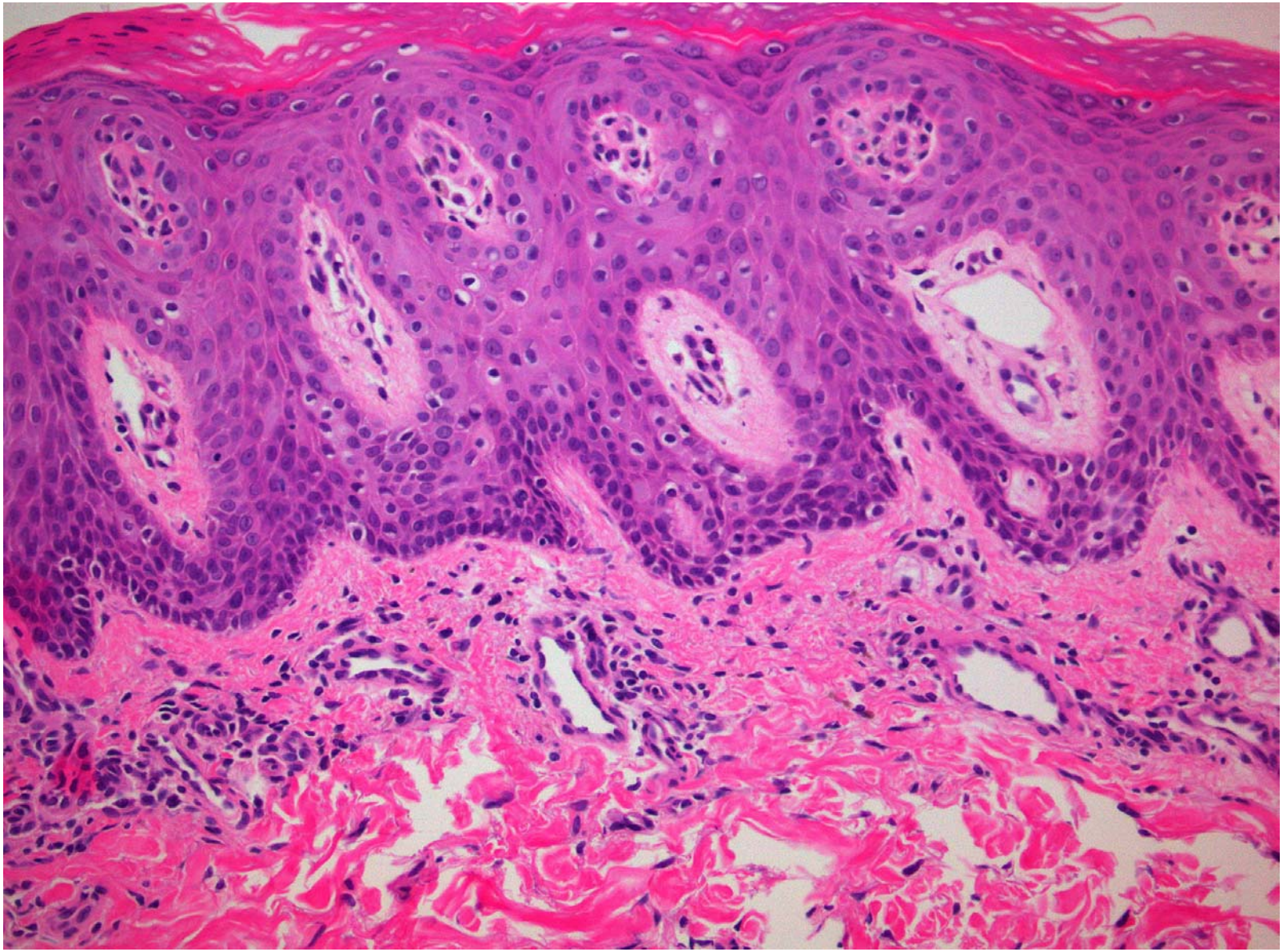
2. Η προηγηθείσα θεραπεία πιθανά τροποποιεί την ιστολογική εικόνα.



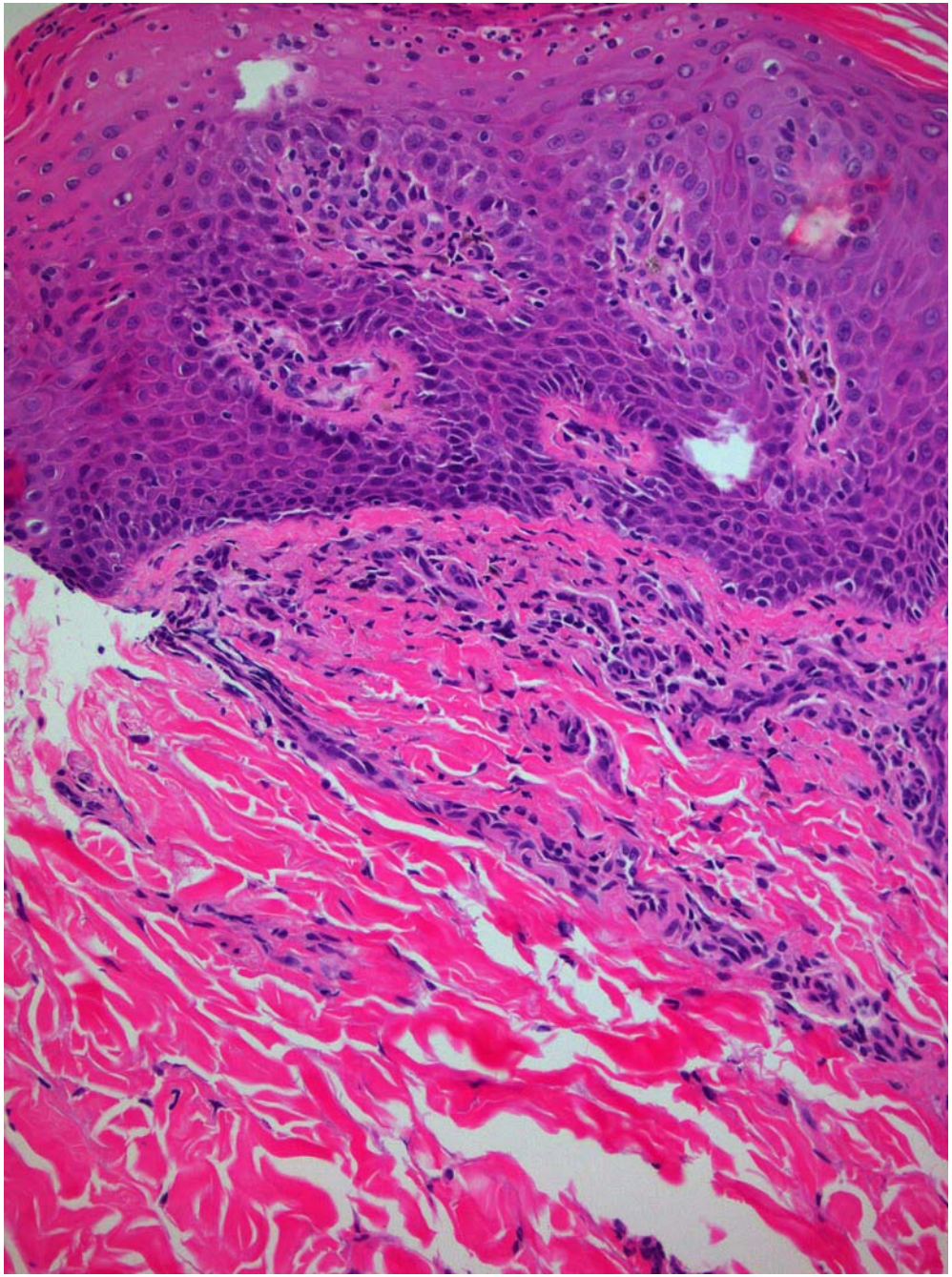
Εστιακή απώλεια της κοκκώδους στιβάδας, παρακεράτωση της επιδερμίδας [H/E x 10]



Πάχυνση της επιδερμίδας, με υπερπλασία και επιμήκυνση των επιδερμιδικών ακρολοφιών. [H/E x 10]



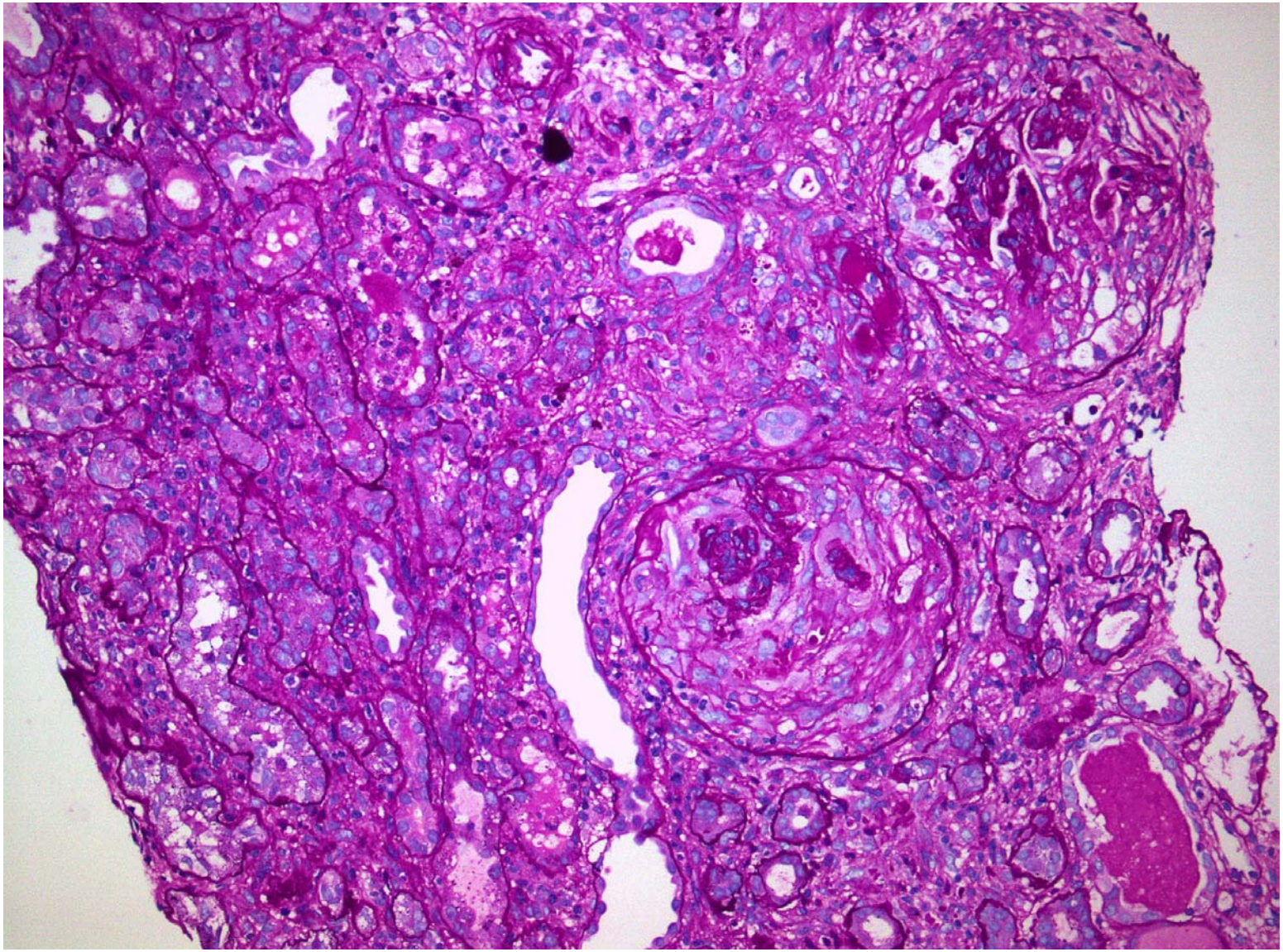
Αυξημένη αγγειοβρίθεια και αύξηση στο μέγεθος των θηλών του χορίου μεταξύ των επιμηκυσμένων επιδερμιδικών ακρολοφιών
[H/E x 10]



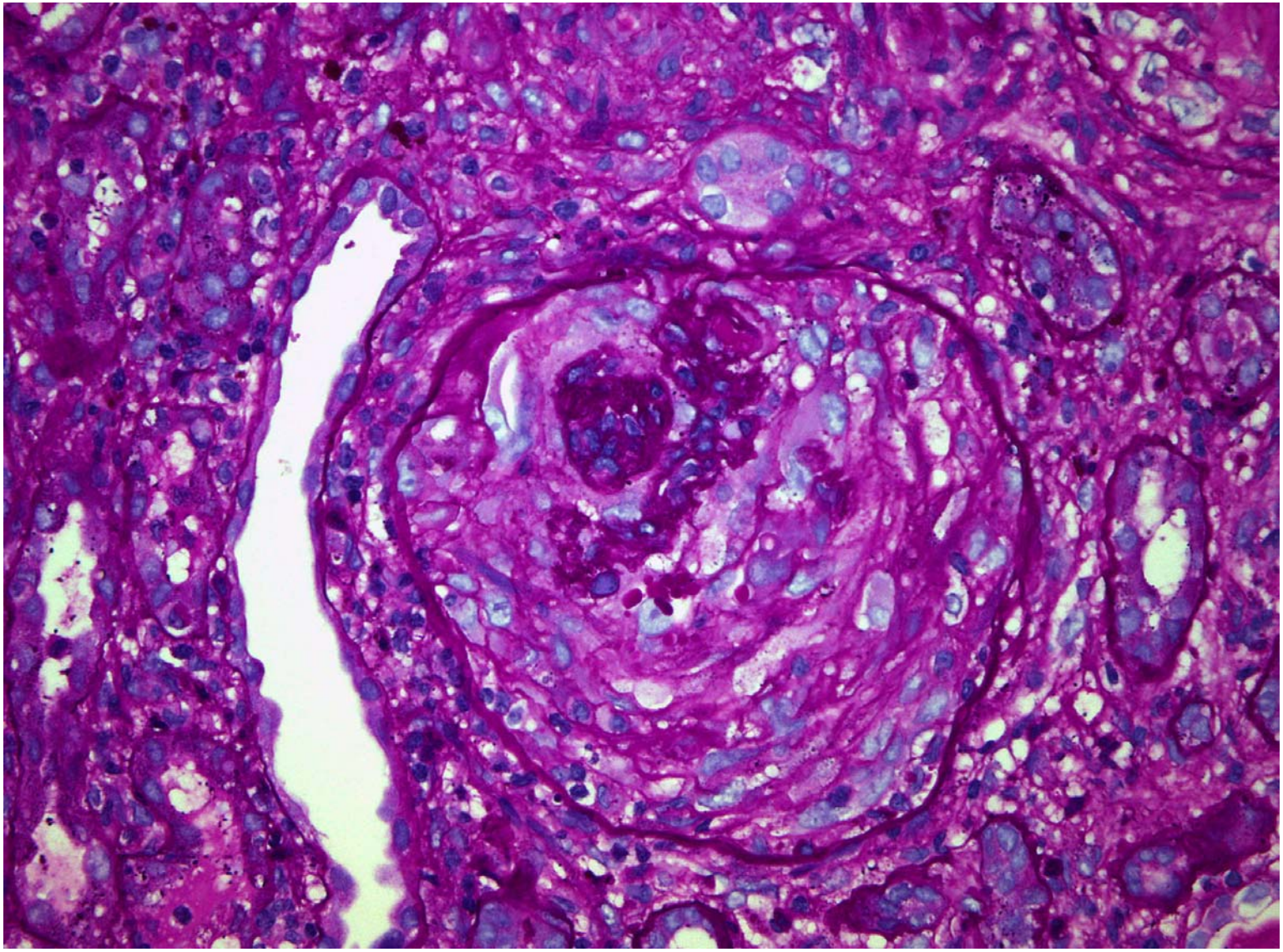
Ήπια-μέτρια περιαγγειακή φλεγμονώδης διήθηση πέριξ των αιμοφόρων αγγείων του θηλώδους χορίου από λεμφοκύτταρα και σπάνια ουδετερόφιλα, διάχυτη ίνωση του χορίου [H/E x 10]

ΒΙΟΨΙΑ ΝΕΦΡΟΥ

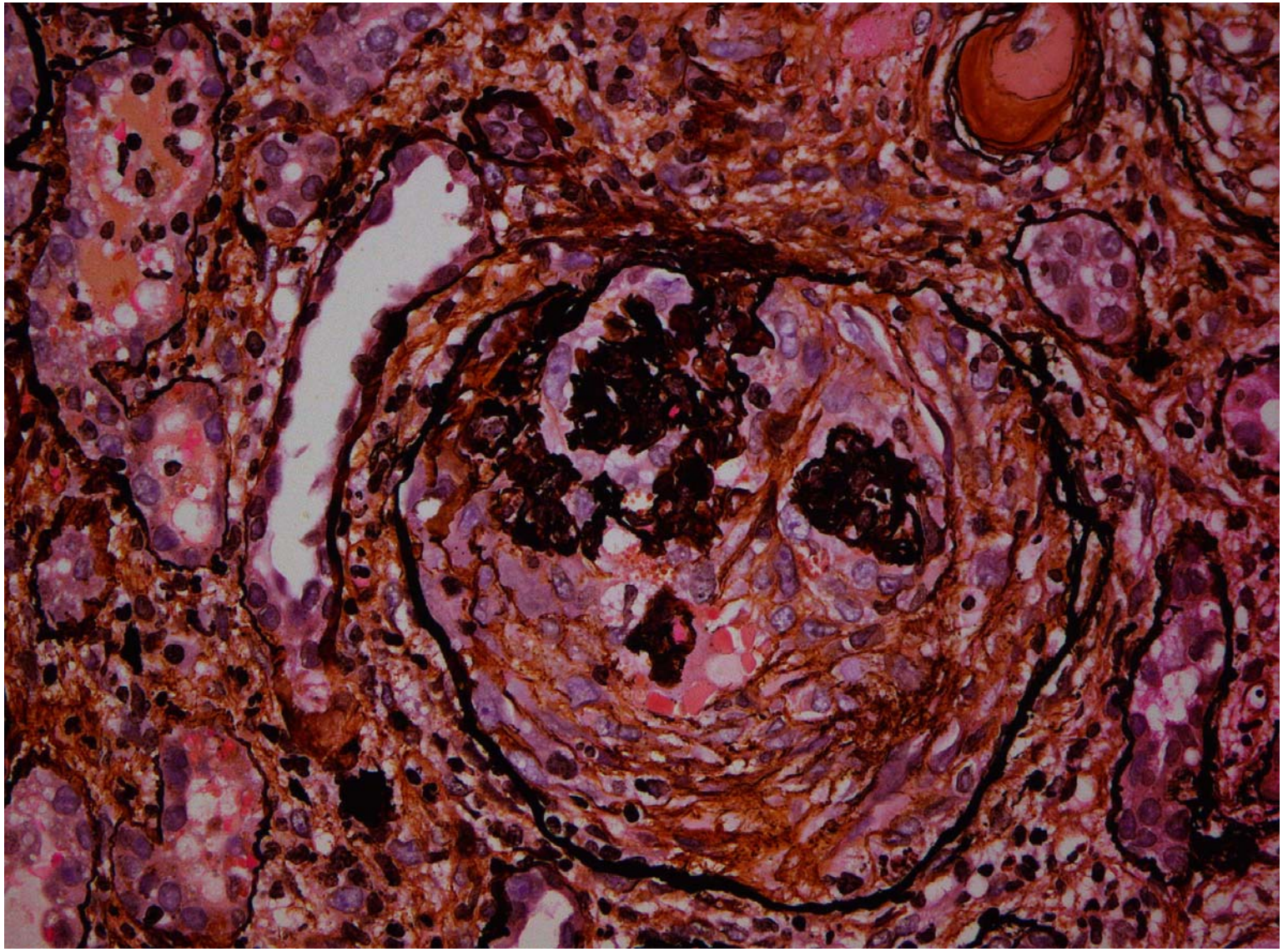
Πρόσφατες και γενικευμένες αλλοιώσεις **εξωτριχοειδικής σπειραματονεφρίτιδας** [crescentic glomerulonephritis] στο 83.3% περίπου του συνόλου των λειτουργικών σπειραμάτων με ανοσοφαινοτυπικά ευρήματα συμβατά **ανοσοπενικής σπειραματονεφρίτιδας** [pauci-mmune / ANCA-mediated Crescentic Glomerulonephritis] οι οποίες χαρακτηρίζονται από την ανάπτυξη πρόσφατων κυτταροβριθών μηνοειδών σχηματισμών και τμηματικών νεκρωτικών αλλοιώσεων στα σπειράματα.
Ήπια ευρήματα σπειραματοσκλήρυνσης [7.7% του συνόλου των σπειραμάτων] τα οποία φαίνονται συμβατά με την ηλικία της ασθενούς (8.5%).
Συνυπάρχουν αξιοσημείωτες αλλοιώσεις διάμεσης - σωληναριακής νεφρίτιδας.



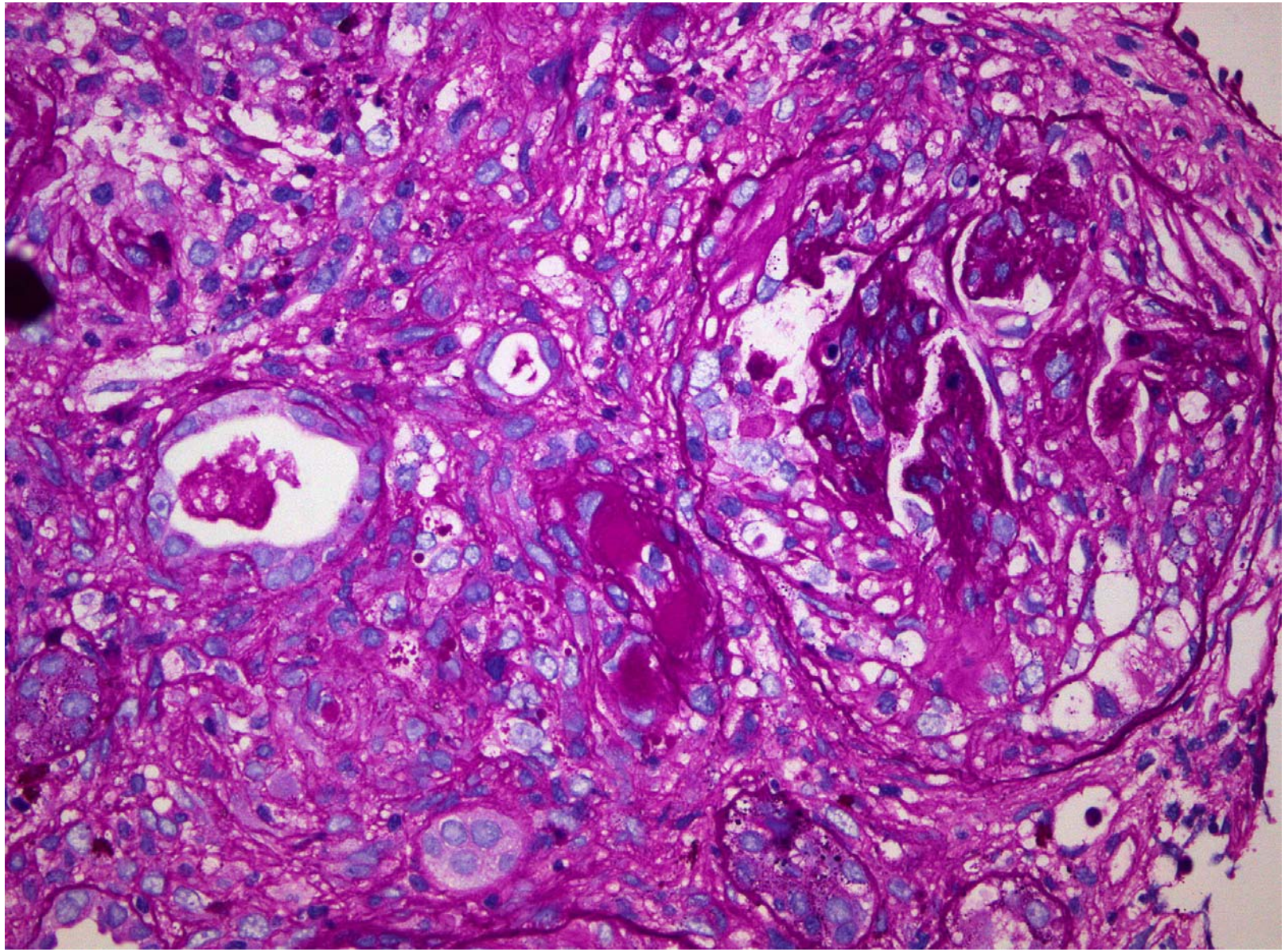
Αλλοιώσεις εξωτριχοειδικής σπειραματονεφρίτιδας – παρουσία πρόσφατων και ευμεγεθών κυτταροβριθών μηνοειδών σχηματισμών [PAS x 10]



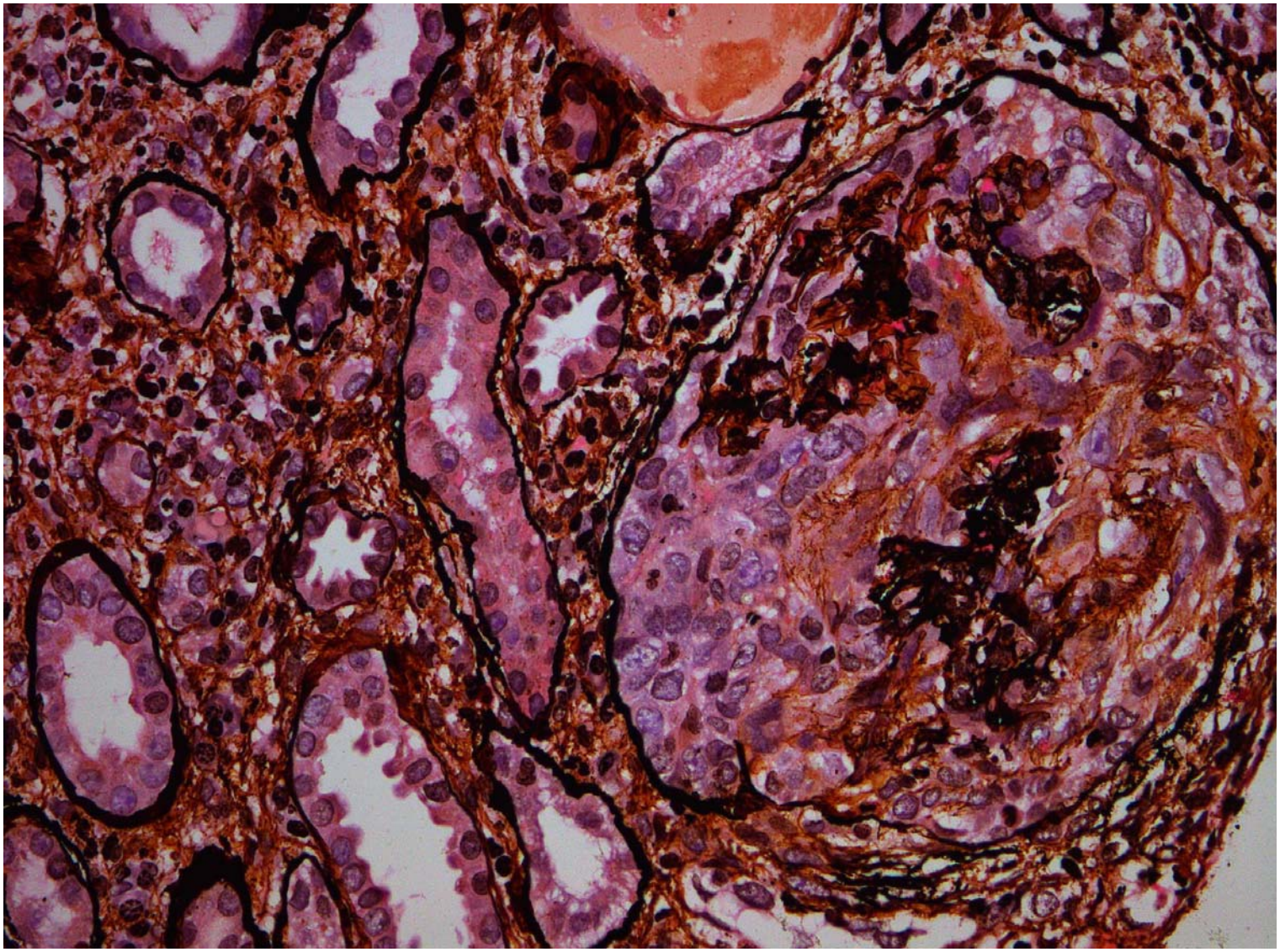
Διόγκωση των σπειραμάτων λόγω των μηνοειδών σχηματισμών. [PAS x 20]



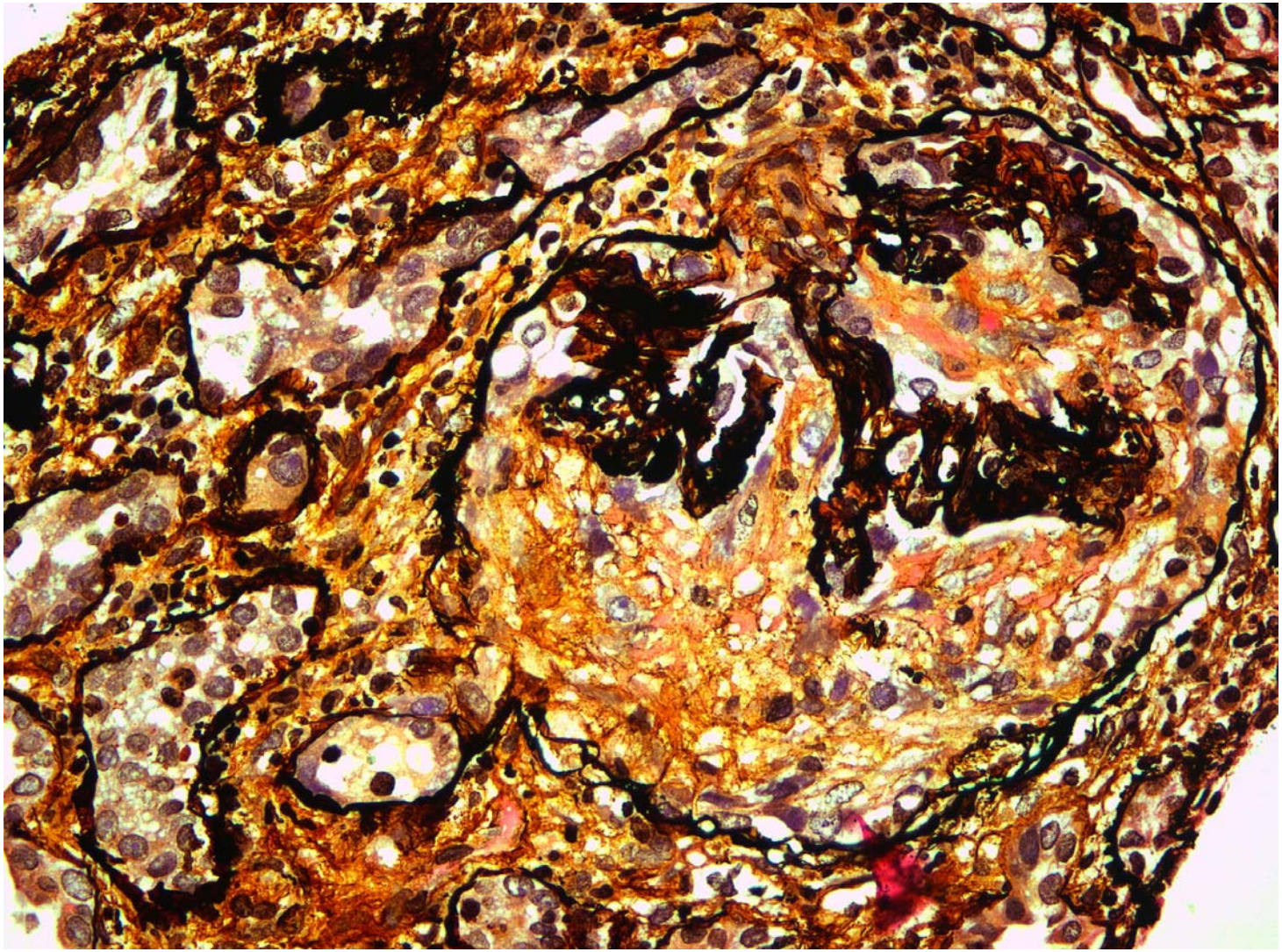
Ινιδοειδής νέκρωση και σύμπτωση των τριχοειδικών τοιχωμάτων. [Silver stain x 200]



Αξιοσημείωτη περισπειραματική φλεγμονώδης διήθηση [PAS x 20]



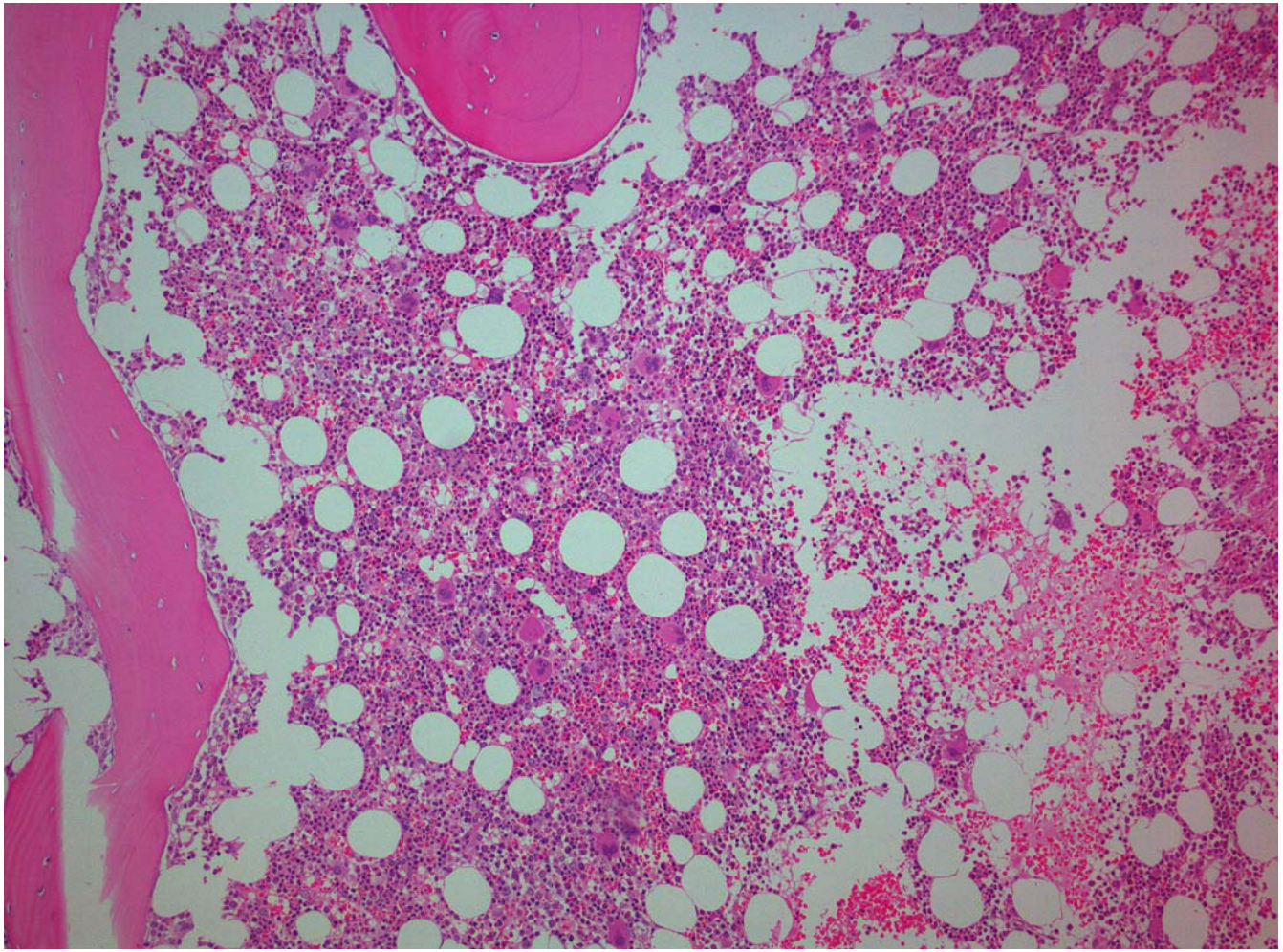
Ινιδοειδής νέκρωση και σύμπτωση των τριχοειδικών τοιχωμάτων.
[Silver stain x 400].



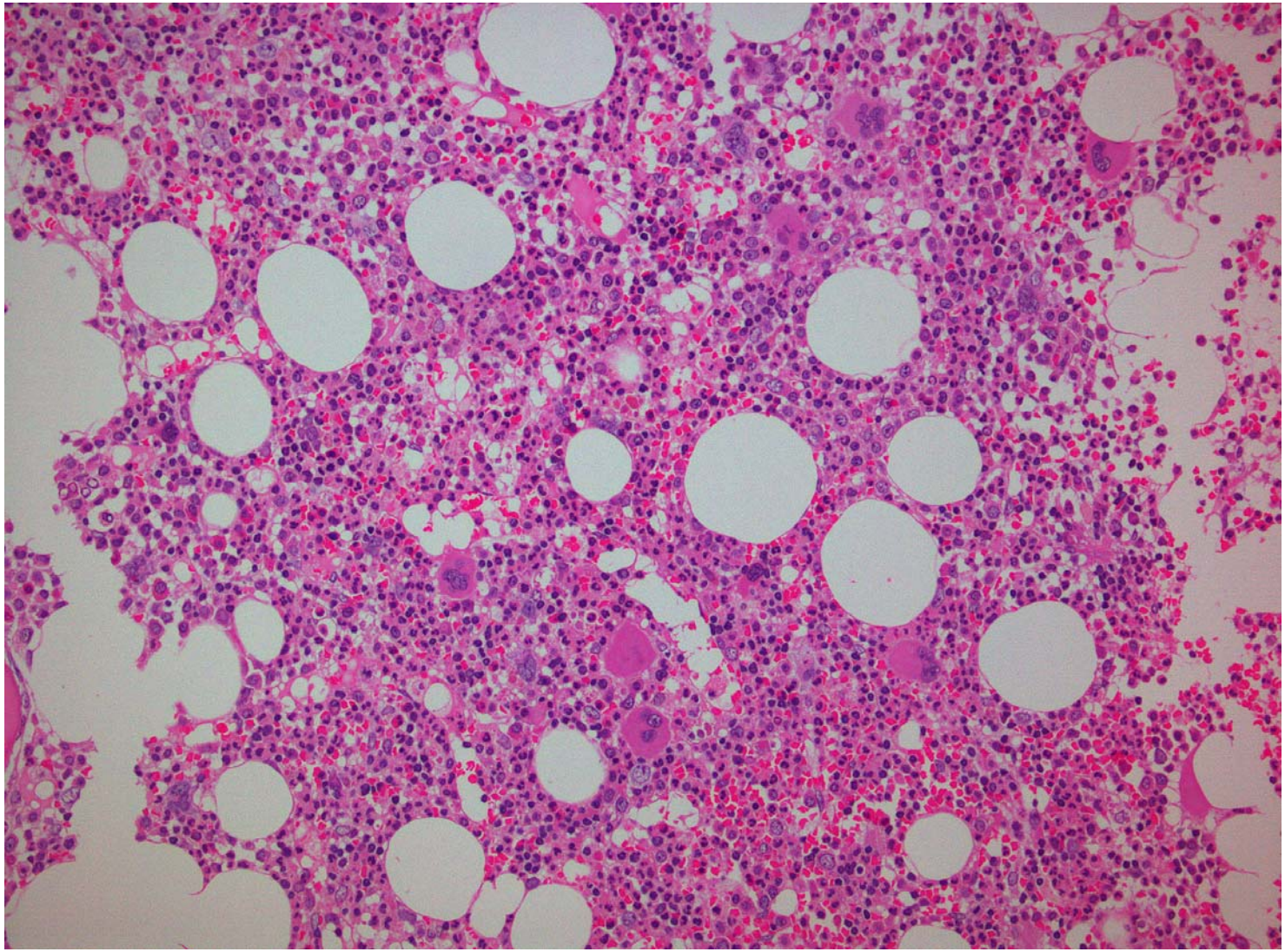
Ινιδοειδής νέκρωση και σύμπτωση των τριχοειδικών τοιχωμάτων[Silver stain x 400]

ΟΣΤΕΟΜΥΕΛΙΚΗ ΒΙΟΨΙΑ

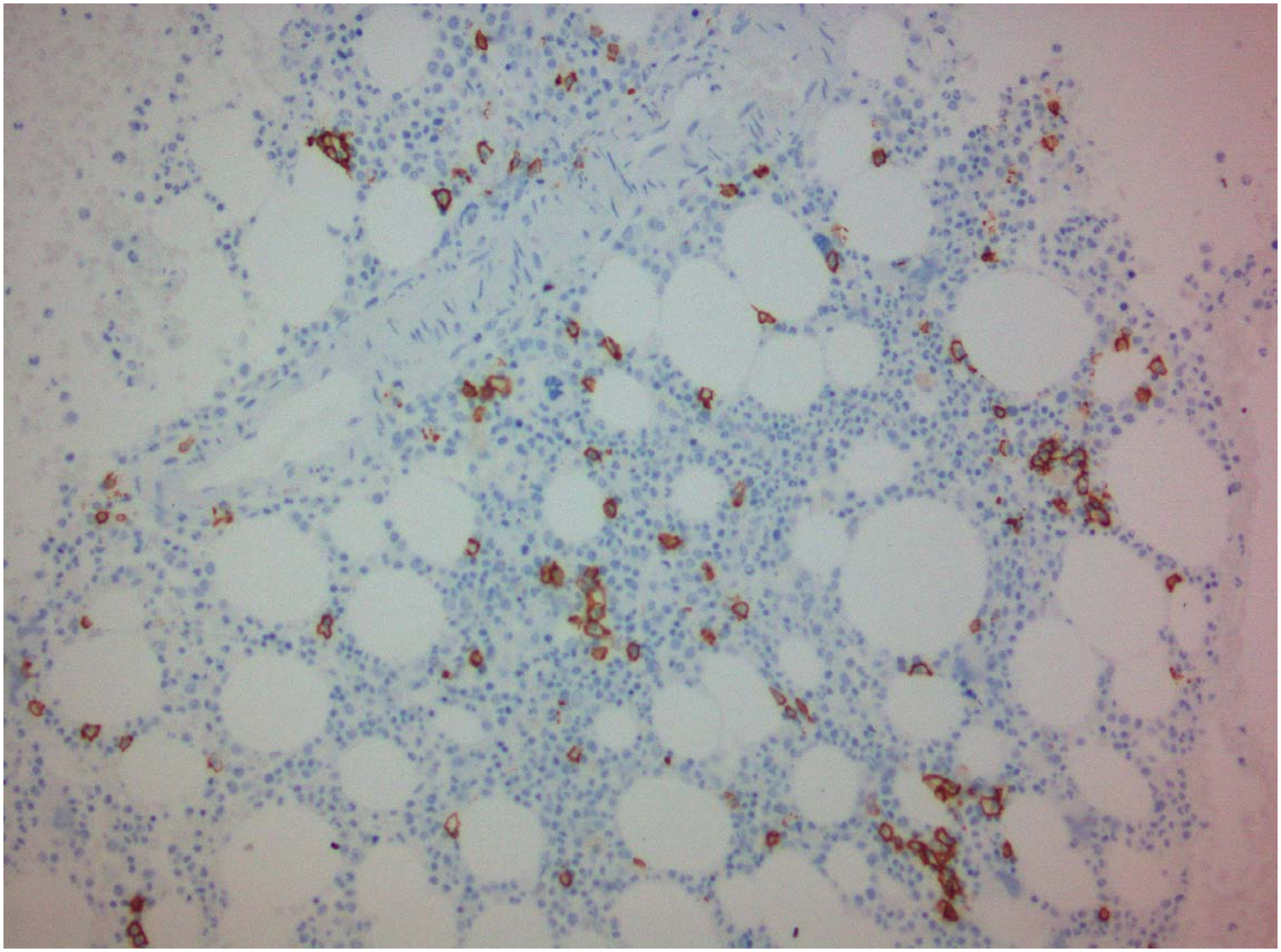
Τα επί μέρους ανοσομορφολογικά ευρήματα θεωρούνται μάλλον συμβατά με **μονοκλωνική γαμμασφαιρινοπάθεια αβέβαιης βιολογικής συμπεριφοράς**



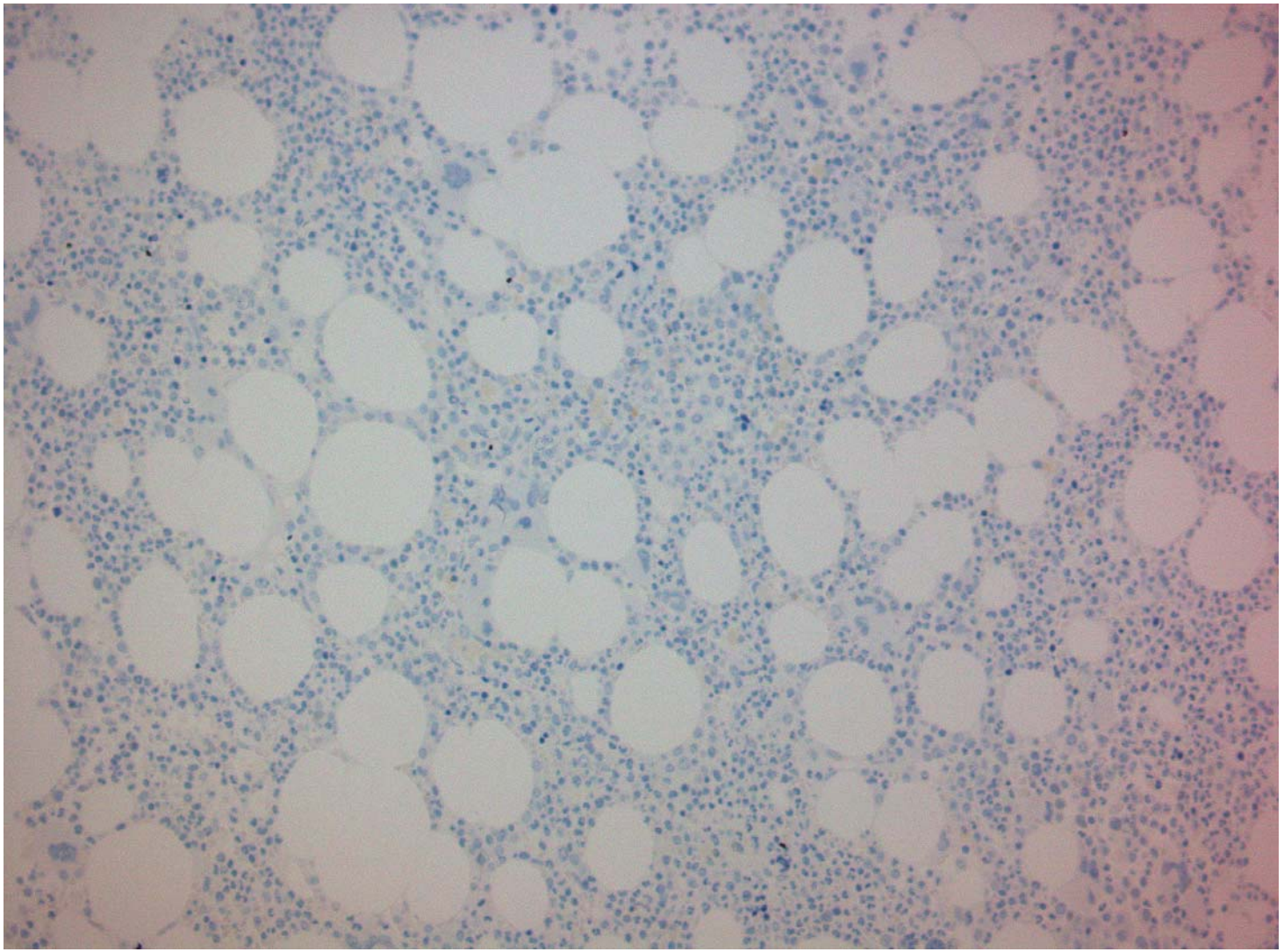
Οστίτης ιστός σπογγώδους τύπου ο οποίος περιλαμβάνει πολλούς μυελοχώρους και φέρει αιμοποιητικό μυελό με μέτρια κυτταροβρίθεια [H/E x4]



Οι κυτταρικές σειρές αντιπροσωπεύονται και ωριμάζουν με διατήρηση της βασικής αρχιτεκτονικής και χωροταξίας. [H-E x 10]



Πλασματοκύτταρα ωρίμου τύπου με ελφρά υπεροχή των παραγόντων κ έναντι λ ελαφρών αλύσεων (IgA-κ) τα οποία αναπτύσσονται με περιαγγειακή μεμονωμένη και σπάνια σε αθροίσεις κατανομή. [CD138 x 10].



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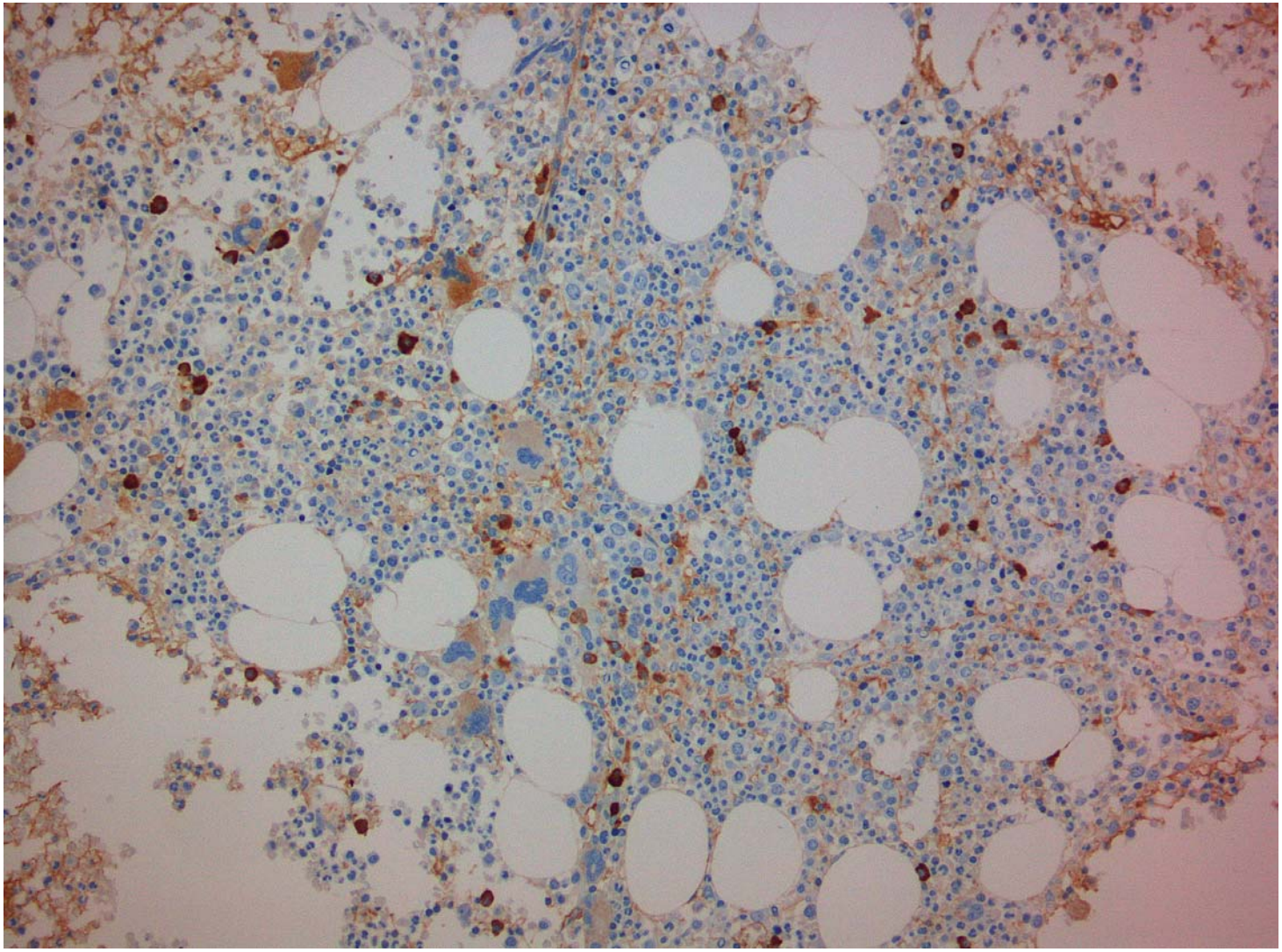

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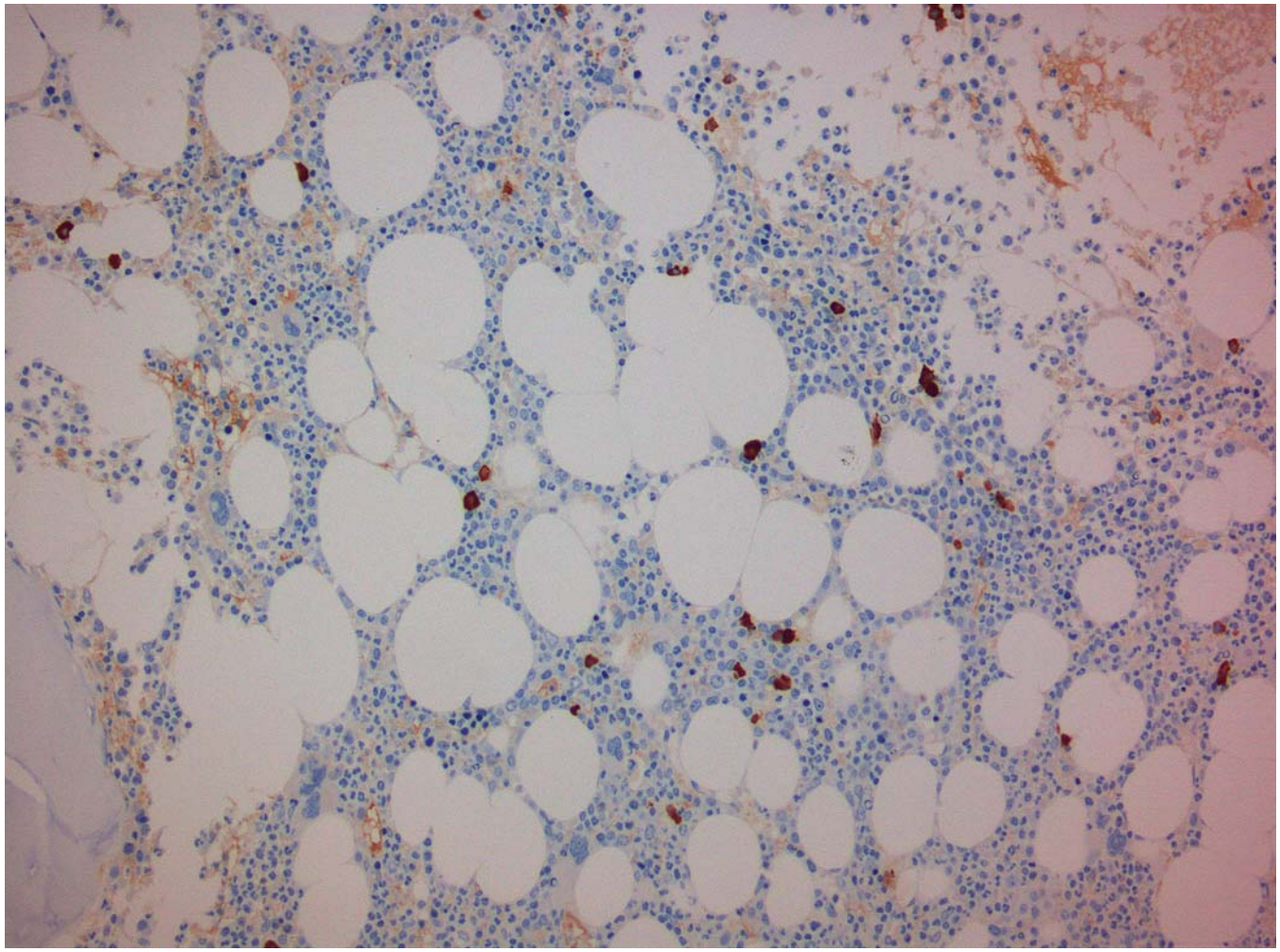

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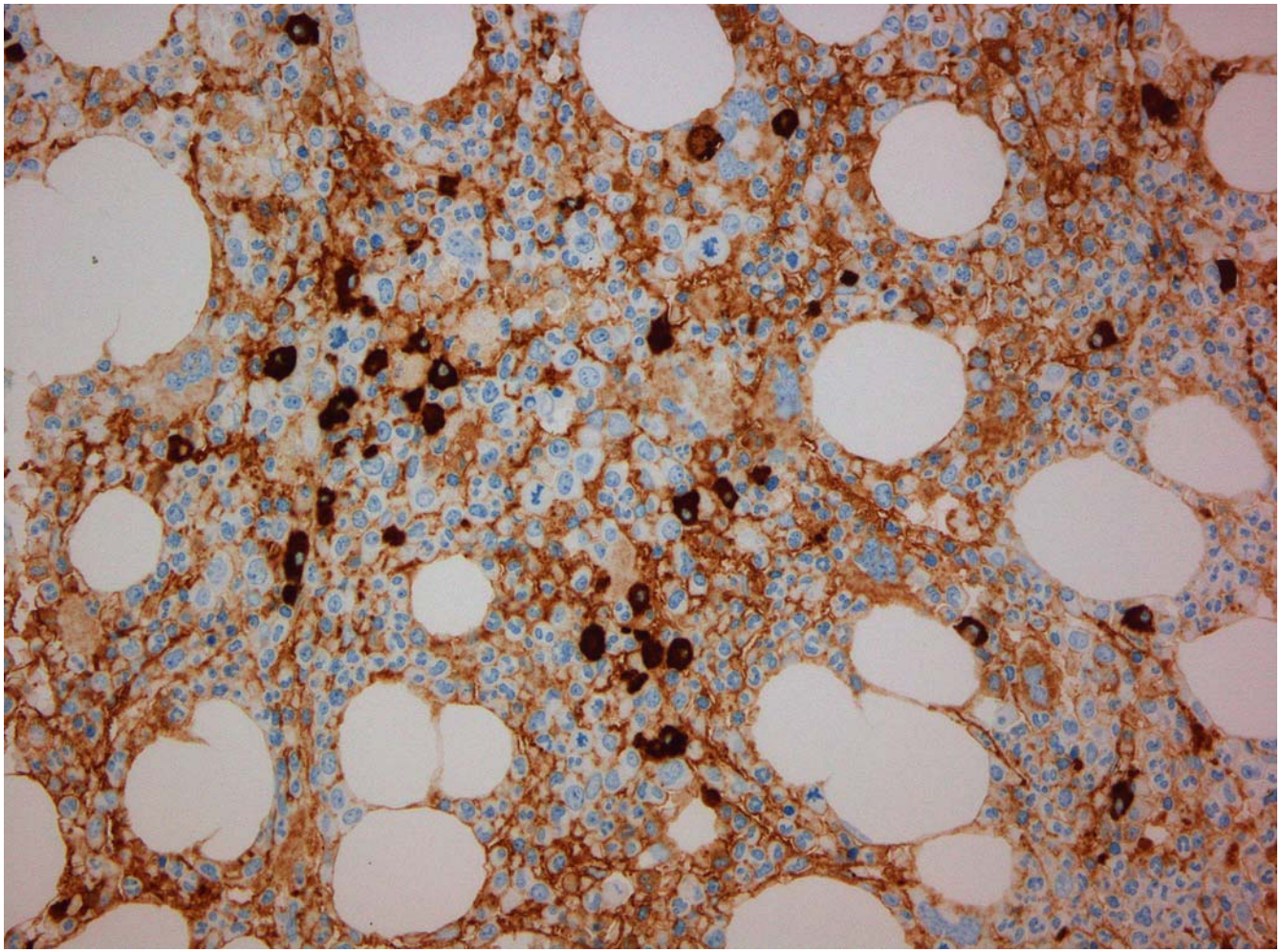

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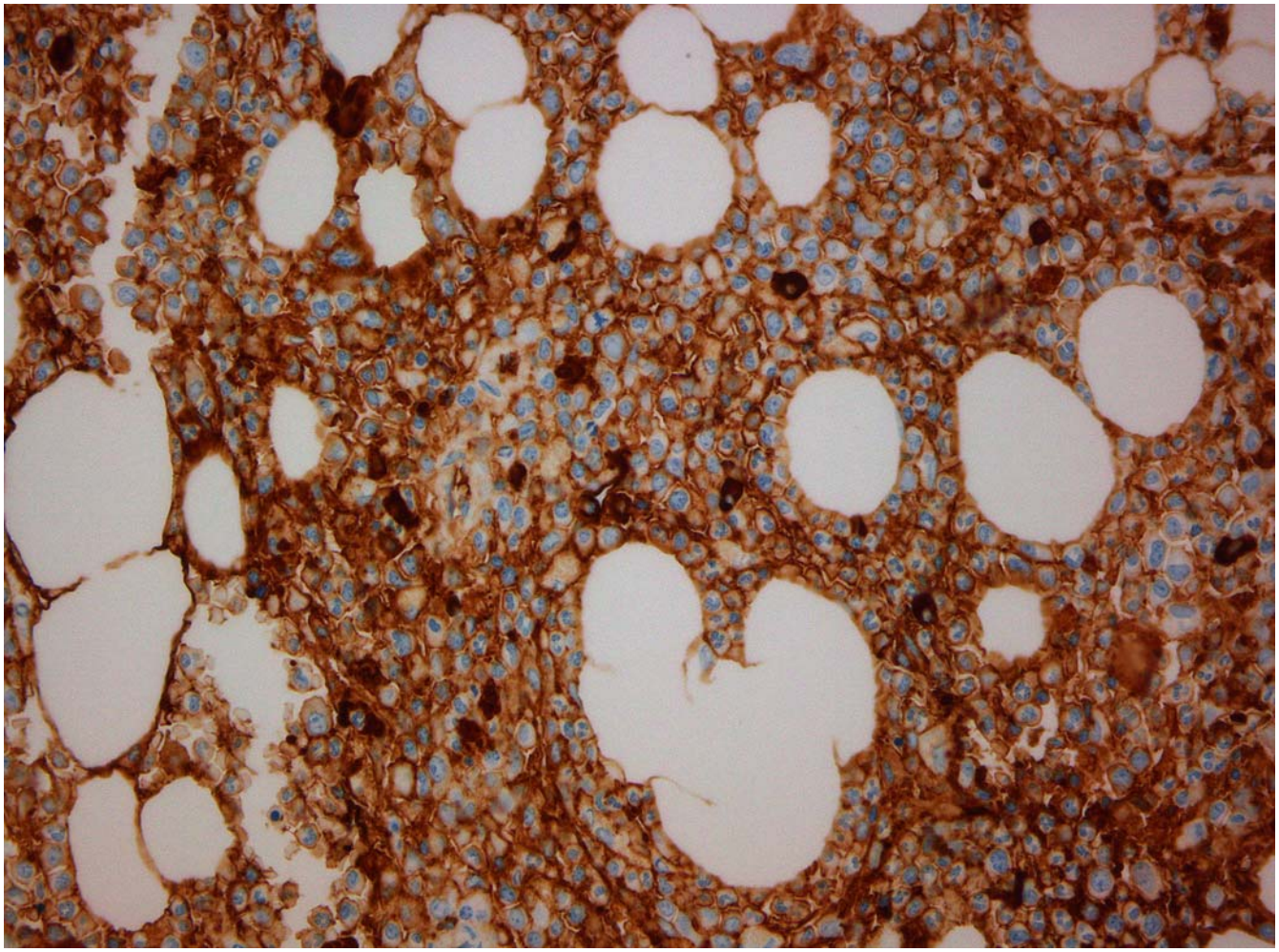
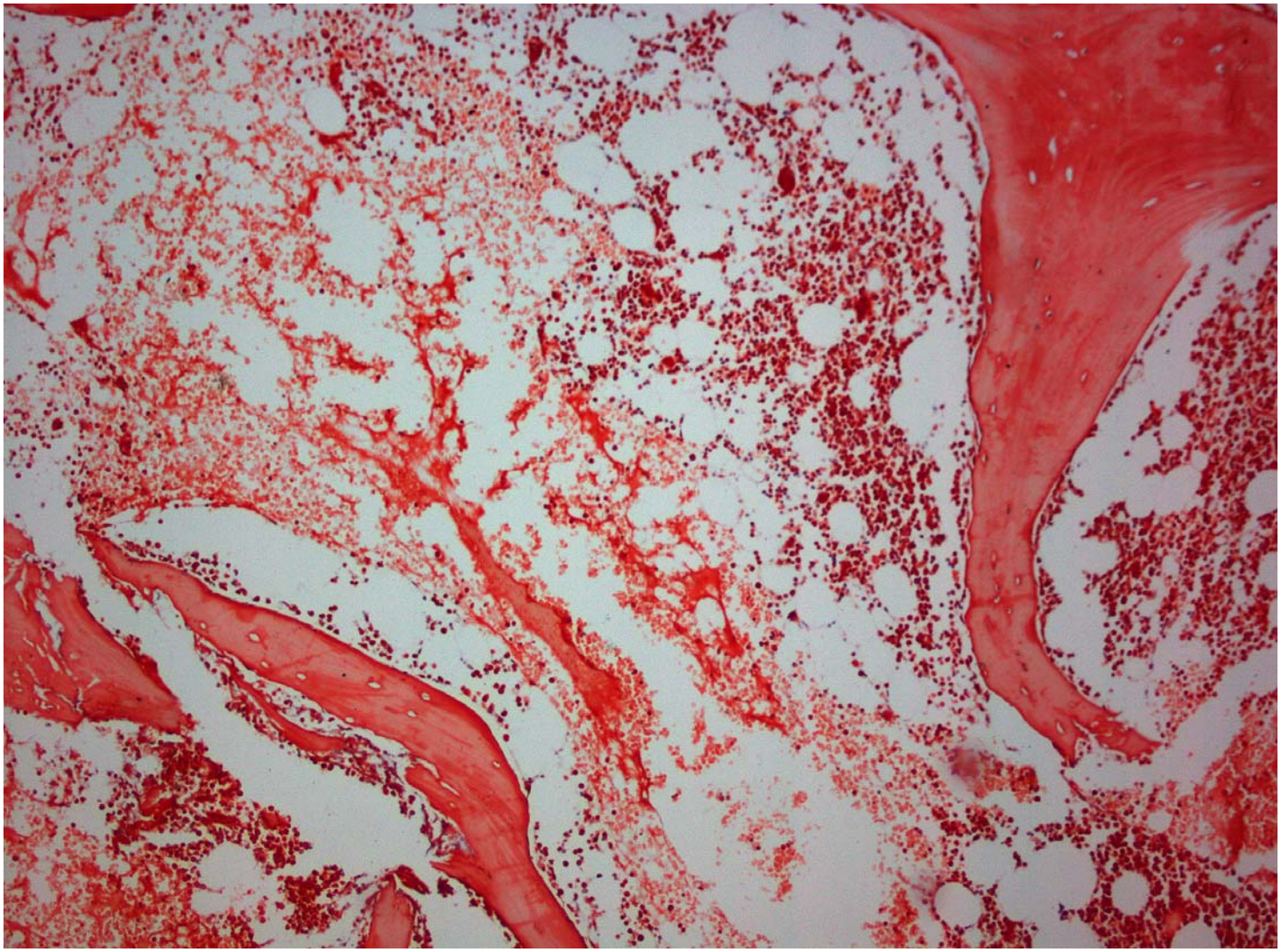


Πλασματοκύτταρα ωρίμου τύπου με ελφρά υπεροχή των παραγόντων κ έναντι λ ελαφρών αλύσεων (IgA-κ) τα οποία αναπτύσσονται με περιαγγειακή μεμονωμένη και σπάνια σε αθροίσεις κατανομή. [IgG x 10].



Ο έλεγχος αμυλοειδούς δεν έδωσε αποτελέσματα. [Congo Red x10]

•Η ανοσοπενική εξωτριχοειδική σπειραματονεφρίτις συνδέεται σε ποσοστό 85-95% με κυκλοφορούντα ANCA.

Heptinstall's Pathology of the Kidney, 7th ed

•Η ανοσοπενική εξωτριχοειδική σπειραματονεφρίτις έχει αναφερθεί (με αιτιολογική συσχέτιση;) σε σχέση με μία σειρά νοσημάτων του συνδετικού ιστού (π.χ. ΣΕΛ, σ. Sjogren, κ.τ.λ.).

Yeturi et al, Case Reports in Rheumatology Volume 2016, Article ID 9070487

•Όπως επίσης και σε σχέση με λήψη anti-TNF αγωγής.

Stokes et al, Nephrol Dial Transplant (2005) 20: 1400–1406

•Τα ευρήματα, ωστόσο, σχετικά με την συσχέτιση ψωρίασης και νεφρικής βλάβης είναι υπό συζήτηση…

Tehranchinia et al, Hindawi e Scientific World Journal Volume 2018

•… εκτός αν ο ασθενής έχει αναπτύξει ψωριασική αρθρίτιδα.

Khan et al, Hindawi International Journal of Inflammation Volume 2017

•Υπάρχουν μεμονωμένα case reports ανοσοπενικής εξωτριχοειδικής σπειραματονεφρίτιδας με συνυπάρχουσα ψωρίαση.

Prasad et al, Pediatr Nephrol (2011) 26:1173–1174

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ

Definitions of ANCA-associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis based on the 2012 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

ANCA-associated vasculitis (AAV)

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add

a prefix indicating ANCA reactivity, for example, PR3-ANCA, MPO-ANCA, ANCA-negative.

Microscopic polyangiitis (MPA)

Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.

Granulomatosis with polyangiitis (GPA)

Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to small vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.

Modified from Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1-11.ANCA-associated vasculitis (AAV)

ANCA Serology

- ANCA are specific for proteins in the cytoplasmic granules of neutrophils and the lysosomes of monocytes.
- Although ANCA are far more frequent in pauci-immune small-vessel vasculitis and glomerulonephritis, ANCA are identified in the serum of approximately one third of patients with anti-GBM disease .
- Two major antigen specificities for ANCA are seen in patients with pauci-immune crescentic glomerulonephritis and small-vessel vasculitis. These two specificities cause two staining patterns, cytoplasmic (c-ANCA) and perinuclear (p-ANCA), when ANCA are detected by indirect immunofluorescence microscopy.
- The most common c-ANCA specificity is for proteinase 3 (PR3-ANCA), and the most common p-ANCA specificity is for myeloperoxidase (MPO-ANCA).
- Dual positivity for both MPO-ANCA and PR3-ANCA is rare except in the setting of drug-induced ANCA.
- Patients with active GPA usually have PR3-ANCA.
- Patients with MPA have slightly more MPO-ANCA than PR3-ANCA, and patients with EGPA and renal-limited pauci-immune crescentic glomerulonephritis have predominantly MPO-ANCA

PATHOLOGIC FINDINGS

- **Light Microscopy**
- **Glomeruli**
- The hallmark histologic lesions of **acute** pauci-immune ANCA glomerulonephritis are **crescents** and **fibrinoid necrosis**, which occur at the same frequency irrespective of the presence or absence of associated systemic vasculitis.
- The glomerular inflammation is accompanied by proportional nonspecific tubulointerstitial inflammatory lesions.
- Eisenberger et al. compared glomerular crescents, necrosis, and sclerosis in patients with **ANCA-negative** pauci-immune glomerulonephritis and patients with **ANCA-positive** pauci-immune glomerulonephritis and found no significant difference, which corresponds to our experience.
- The extent of crescent formation is not different between patients with PR3-ANCA versus MPO-ANCA.
- Vizjak et al. (11) observed periglomerular **granulomatous** inflammation more often in MPO-ANCA disease than in PR3-ANCA disease, which indicates that this reaction is not related to the type of granulomatous inflammation that corresponds to GPA.

Light Microscopy

Periglomerular granulomatous inflammation probably is not specific for pauci-immune crescentic glomerulonephritis or ANCA glomerulonephritis, but this is controversial. Some investigators have reported periglomerular granulomatous inflammation only in patients with ANCA.

The histologic features of renal-limited pauci-immune crescentic glomerulonephritis are indistinguishable from those of pauci-immune crescentic glomerulonephritis that occurs as a component of systemic vasculitis.

Not surprisingly given their relative frequency, the immune complex diseases that have been reported most often in **association with ANCA** are **membranous glomerulonephritis, IgA nephropathy, diabetic glomerulosclerosis, and lupus glomerulonephritis.**

With time, the necrotic glomerular lesions of pauci-immune crescentic glomerulonephritis heal as **segmental or global sclerosis**

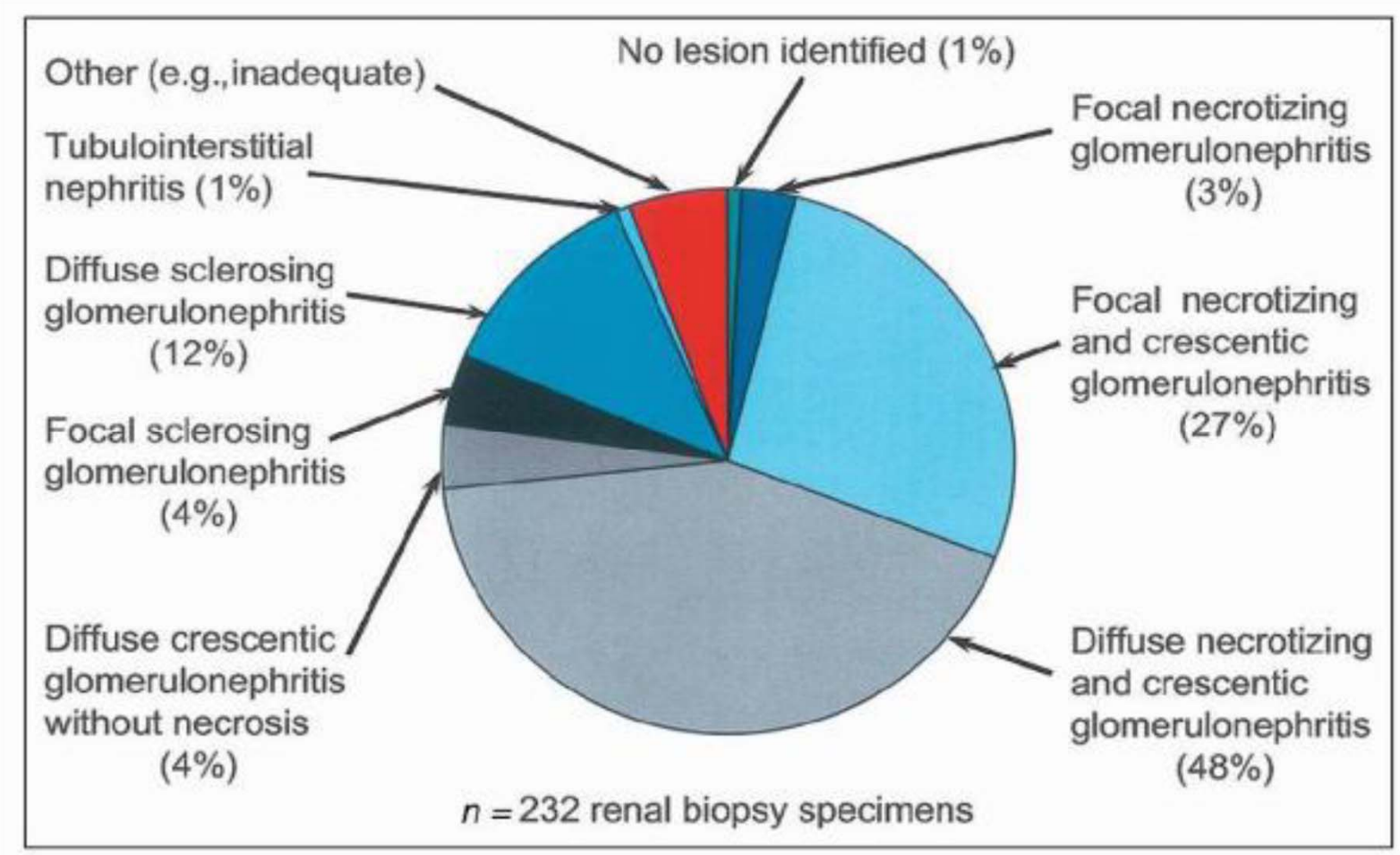
The proportion of sclerotic glomeruli at the time of biopsy tends to be higher in MPO-ANCA glomerulonephritis than in PR3-ANCA glomerulonephritis.

European Vasculitis Study Group (EUVAS) patient cohorts.
This classification system categorizes ANCA pauci-immune glomerulonephritis into 4 classes based on the histopathologic glomerular findings, that is, focal, crescentic, sclerotic, or mixed based on the criteria given below.
Of 100 biopsies with ANCA pauci-immune glomerulonephritis, 13 were classified as **sclerotic** (≥50% globally sclerotic glomeruli), 16 as **focal** (≥50% normal glomeruli), 55 as **crescentic** (≥50% of glomeruli with cellular crescents), and 16 as **mixed** (greater than 50% of glomeruli with lesions but no predominance of crescentic or sclerotic glomeruli).

Renal survival correlated with these classes.
Renal survival at **1 year** was 93% for the focal class, 84% for crescentic class, 69% for the mixed class, and 50% for the sclerotic class.

Renal survival at **5 years** was 93% in the focal class, 76% in crescentic class, 61% in mixed class, and 50% in sclerotic class.

Several additional validations of the classification system have confirmed its utility with the **focal class consistently having the best outcome and the sclerotic class the worst outcome**



Categorization of the pathologic findings in 232 renal biopsy specimens from **ANCA-positive** patients who underwent renal biopsy evaluation at the University of North Carolina Nephropathology Laboratory because of clinical evidence for renal disease. Patients categorized as having necrotizing and crescentic glomerulonephritis often also had some degree of glomerular sclerosis. Patients categorized as having sclerosing glomerulonephritis had no necrosis, and any crescents were fibrocellular or fibrotic.

Arteries, arterioles, and medullary vasa recta should be carefully examined in a specimen that has pauci-immune crescentic glomerulonephritis because of the possibility of accompanying necrotizing small-vessel vasculitis that can cause renal arteritis, arteriolitis, and medullary angiitis.

The interlobular arteries are the most commonly affected arteries, but any artery may be involved. The necrotizing arteritis of pauci-immune small-vessel vasculitis is histologically indistinguishable from the necrotizing arteritis of polyarteritis nodosa.

Vizjak et al. identified active vasculitis in 23% of 55 patients with PR3-ANCA glomerulonephritis and 23% of 74 patients with MPO-ANCA glomerulonephritis. This is an underestimate of the frequency of arteritis because the lesions always are focal, and renal biopsy specimens provide only a very small sampling of renal arteries.

The severity of medullary angiitis does not correlate with the severity of glomerulonephritis or the presence of cortical vasculitis. Severe medullary angiitis results in ischemia and coagulative necrosis that may lead to sloughing of the necrotic papillary tip.

Extrarenal Pathology

The pathologic features of the necrotizing vasculitis lesions of MPA, GPA, and EGPA are the same in other organs as they are in the kidney.

Histologic demonstration of necrotizing vasculitis alone, however, is not diagnostic for pauci-immune small-vessel vasculitis or for a specific category of ANCA small-vessel vasculitis without additional serologic, clinical, or pathologic data.

For example, histologically indistinguishable necrotizing arteritis in a biopsy specimen from skeletal muscle, peripheral nerve, or skin can be caused by polyarteritis nodosa, MPA, GPA, and EGPA.

Similarly, histologically indistinguishable leukocytoclastic angiitis in the dermis can be caused not only by the ANCA small-vessel vasculitides but also by IgA vasculitis (Henoch-Schönlein purpura [HSP]), cryoglobulinemic vasculitis, lupus vasculitis, serum sickness vasculitis, rheumatoid vasculitis, and other small-vessel vasculitides.

Based on a biopsy specimen alone, a pathologist can provide only a descriptive diagnosis (such as necrotizing arteritis or leukocytoclastic angiitis) along with a differential diagnosis of categories of vasculitis that could be causing the lesions.

Hemorrhagic necrotizing pulmonary alveolar capillaritis is a frequent, and often life-threatening, feature of GPA and MPA, but is uncommon in EGPA.

Immunofluorescence Microscopy

There is no standard criterion, however, for where to draw the line between pauci-immune crescentic glomerulonephritis and immune complex crescentic glomerulonephritis with respect to the amount or intensity of glomerular staining for immunoglobulin.

There is an inverse relationship between the amount of staining for immunoglobulin in a specimen with crescentic glomerulonephritis and the frequency of ANCA positivity.

Thus, the more pauci-immune the specimen is, the more likely the patient is to have ANCA glomerulonephritis.

However, ANCA-positivity does not influence the pathologic diagnosis or clinical management because **ANCA-negative** pauci-immune glomerulonephritis has the same pathologic and clinical features as **ANCA-positive** pauci-immune glomerulonephritis.

An important distinction to make when examining a specimen with pauci-immune crescentic glomerulonephritis is the staining in glomeruli or portions of glomeruli that do not have necrosis or sclerosis versus staining in glomeruli or portions of glomeruli that do have necrosis or sclerosis.

As in other glomerular diseases, areas of glomerular sclerosis have irregular staining for C3, C1q, and IgM.

Foci of glomerular necrosis also have variable staining for C3 and immunoglobulins and marked staining for fibrin.

The staining for immunoglobulin and especially complement often is accentuated and may only be observed in areas of segmental necrosis or sclerosis.
This greater correspondence with sites of injury differs from immune complex-mediated glomerulonephritis and anti-GBM glomerulonephritis in which the staining for immunoglobulin and complement is as strong if not stronger in glomeruli and glomerular segments that do not have injury.
This may result from the difference in pathogenesis with immune deposits preceding the initiation of inflammation in immune complex and anti-GBM disease, versus initiation of immunoglobulin binding and complement activation only at the sites of injury in ANCA disease.
As noted earlier, the definition of “pauci-immune” is somewhat arbitrary. Most pathologists use a staining intensity of 2+ or less as the cutoff point.
When staining for immunoglobulins is present, it may be for any combination of IgG, IgM, or IgA. Staining for IgM is most frequent.
If the patient has IgA nephropathy with extensive necrosis and crescents but is ANCA negative, one can only conjecture about the possibility of concurrent ANCA-negative glomerulonephritis with the IgA nephropathy.
ANCA glomerulonephritis concurrent with membranous glomerulonephritis. Our arbitrary approach is to make the latter diagnosis only if 50% of glomeruli have over 50% of the tufts involved with 2+ or greater granular staining for IgG in a patient with necrosis, crescents, and ANCA.

DIFFERENTIAL DIAGNOSIS

Pauci-immune crescentic glomerulonephritis and pauci-immune small-vessel vasculitis must be distinguished from immune complex-mediated glomerulonephritis and small-vessel vasculitis and **anti-GBM disease**. This may be difficult or impossible by light microscopy alone; however, immunohistology and serology usually result in an actionable diagnosis.

By light microscopy, anti-GBM glomerulonephritis is indistinguishable from pauci-immune crescentic glomerulonephritis because it, too, typically has conspicuous fibrinoid necrosis and crescent formation in the absence of substantial endocapillary hypercellularity or thickening of capillary walls.

The renal pathologic features of **drug-associated ANCA disease** are indistinguishable from those of idiopathic ANCA disease. An unusually high titer of MPO-ANCA should raise suspicion of drug-induced disease.

Propylthiouracil, hydralazine, methimazole, minocycline, and a number of other drugs apparently induce circulating MPO-ANCA and pauci-immune crescentic glomerulonephritis and systemic small-vessel vasculitis.

Cocaine-induced ANCA disease is most likely caused by admixed levamisole.

CLINICAL COURSE, PROGNOSIS, THERAPY, AND CLINICOPATHOLOGIC CORRELATIONS

Pauci-immune crescentic glomerulonephritis, with or without accompanying systemic vasculitis, is an aggressive renal disease that warrants aggressive immunosuppression; however, remission can be induced in most patients with expeditious treatment.
Without treatment, pauci-immune crescentic glomerulonephritis and small-vessel vasculitis have a 1-year mortality of 80%, whereas with treatment, there is a 75% 5-year patient and renal survival.

Patients with MPO-ANCA may have a better prognosis than those with PR3-ANCA even though they have more extensive and more chronic renal disease at presentation.

Patients with PR3-ANCA have more extrarenal organ manifestations and respiratory tract granulomatous inflammation and a greater relapse rate after induction of remission.

Factors that independently correlate with an overall poor outcome include **older age**, **higher serum creatinine** at presentation, and **pulmonary hemorrhage**.

The **pathologic finding** that correlated best with renal function at the time of biopsy and during follow-up was the percentage of histologically **normal glomeruli**.
Other features included **glomerular sclerosis**, **interstitial leukocyte infiltration, tubular necrosis, and tubular atrophy**.
The glomerular filtration rate **(GFR)** at **18 months** after diagnosis correlated best with **interstitial fibrosis and tubular atrophy**, whereas glomerular **crescents and necrosis** correlated with the extent of **recovery of renal function** (i.e., the GFR at 18 month minus the GFR at diagnosis).
Pathologic classification based on the proportions of normal, crescentic, and sclerotic glomeruli helps predict renal outcome , with patients with **≥ 50% normal** glomeruli having the best outcome and patients with **≥ 50% globally sclerotic** glomeruli having the worst outcome.
Berden et al. also evaluated the importance of **tubulointerstitial inflammation** in predicting outcome among patients treated with a **rituximab** based regimen in the Randomized Trial of Rituximab versus Cyclophosphamide in ANCA-Associated Vasculitis trial.
Both CD3(+) T-cell **tubulitis and tubular atrophy** correlated with estimated **GFR at 12 months**; **tubular atrophy remained an independent predictor of renal outcome at 24 months ($P < 0.01$).**
Several studies conclude that **chronic injury** at the time that treatment is begun is **irreversible** and is likely to result in a poor renal outcome if it is severe enough, whereas **active inflammatory lesions** may be suppressed or reversed by treatment and thus are predictors that there will be a response to anti-inflammatory and immunosuppressive treatment.