ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
Ο ΕΥΑΓΓΕΛΙΣΜΟΣ

ΔΩΜΑ 21/11/18

«Άνδρας 73 ετών με ζάλη περιστροφικού τύπου, δυσαρθρία και δυσκαταποσία»

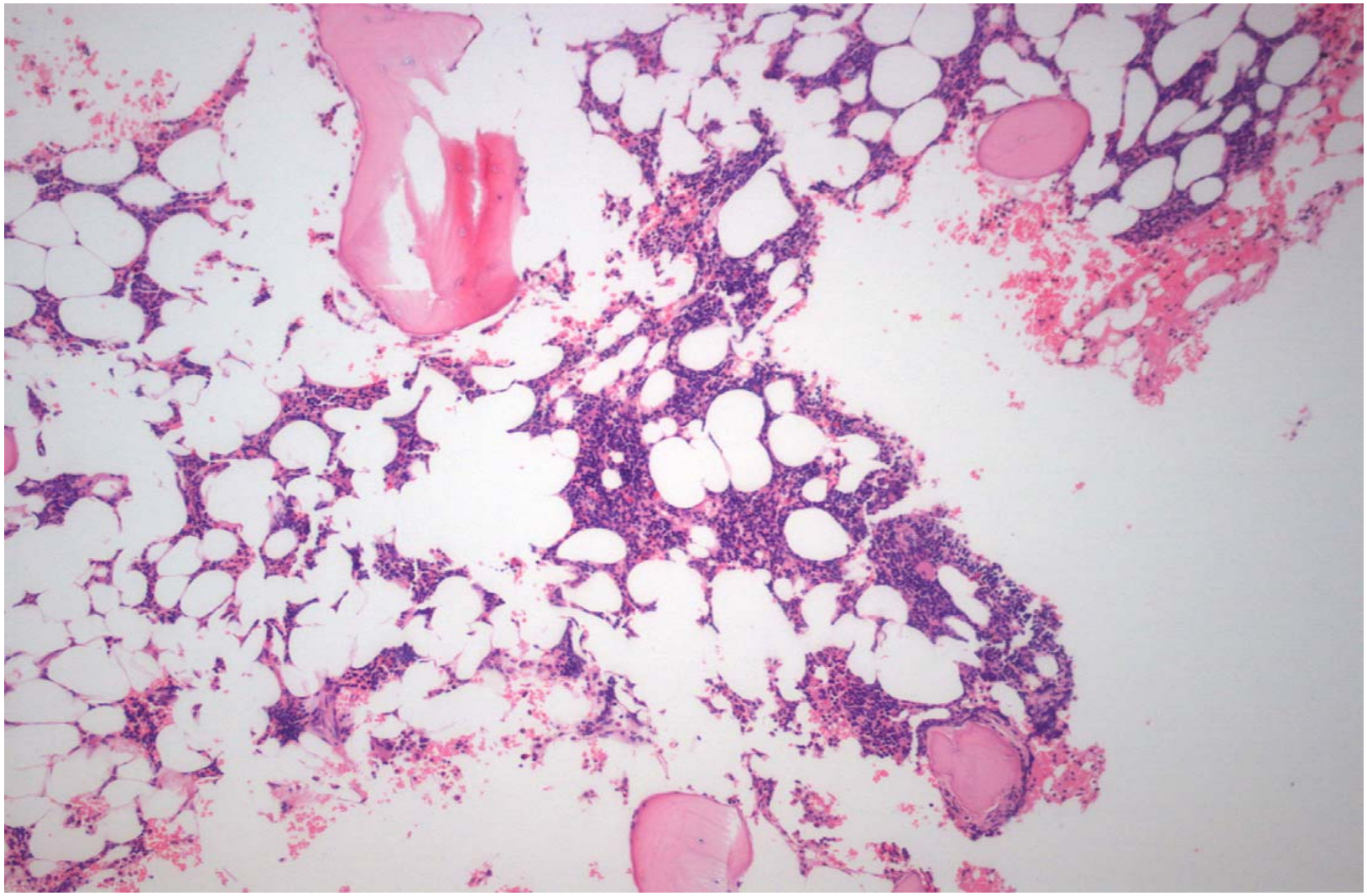
Ανδρέας Παρασκευάς, Ειδικευόμενος Ιατρός
Χριστίνα Βουρλάκου, Διευθύντρια
Γ.Ν.Α. «Ο Ευαγγελισμός», Παθολογοανατομικό τμήμα
Συντονίστρια Διευθύντρια Δ. Ροντογιάννη

1. Διήθηση αιμοποιητικού μυελού από **μη Hodgkin λέμφωμα Β** κυτταρικής προέλευσης με ανοσομορφολογικούς χαρακτήρες συμβατούς με λεμφοκυτταρικό **λέμφωμα από μικρά λεμφοκύτταρα / Β χρόνια λεμφοκυτταρική λευχαιμία** – ταξινόμηση κατά WHO 2017 **CLL/SLL** ICD 0-code 9823/3

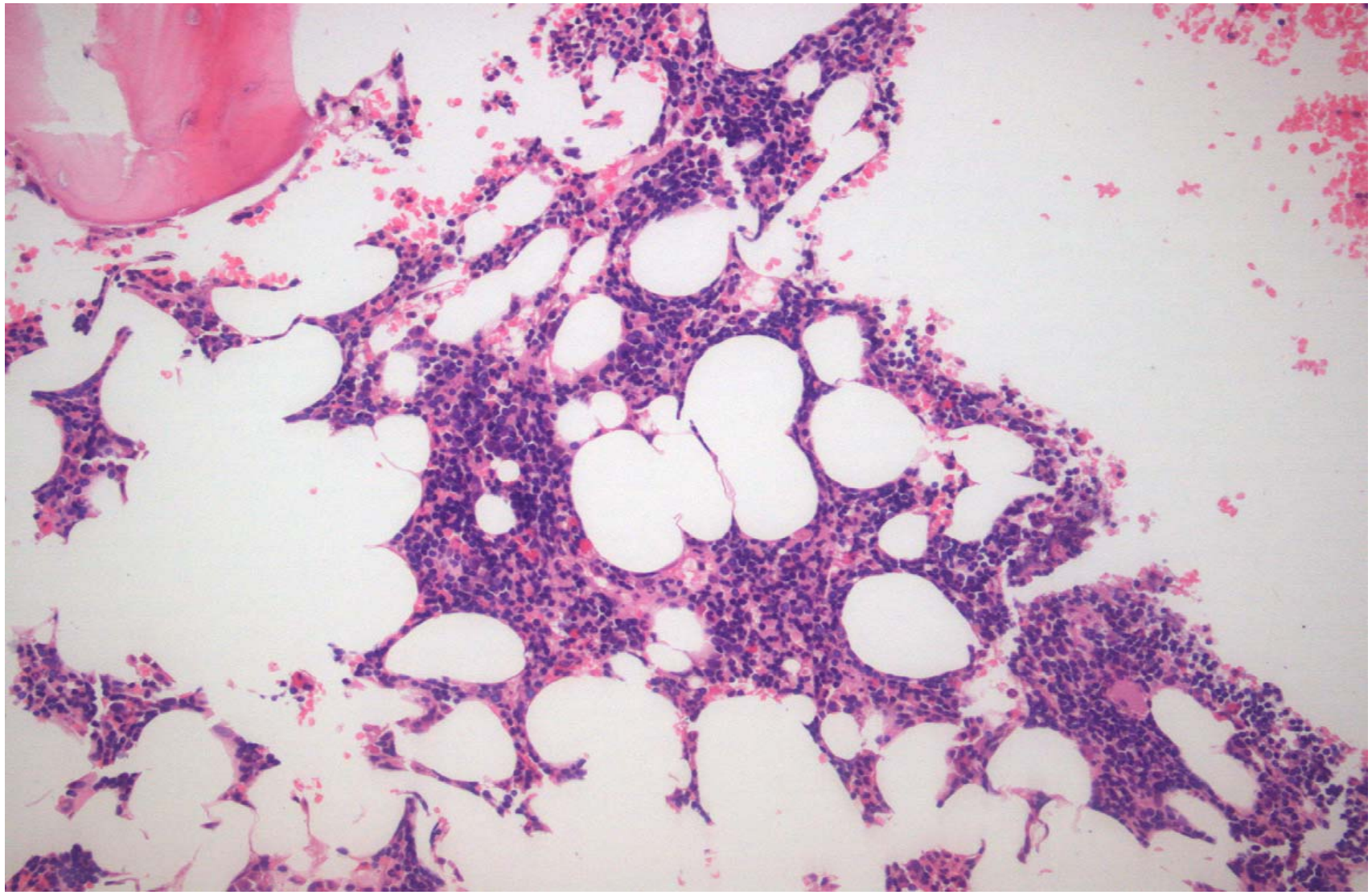
2. Πλασματοκυτταρική **μονοκλωνική παρουσία με παραγωγή λ ελαφράς αλύσσου.**

3. Εναποθέσεις αμυλοειδούς (**Congo red**/πεπολωμένο φώς) περιαγγειακά, σε αγγεία του μυελού και στο περιόστεο.

Συστηματική αμυλοείδωση.



Λεμφοκυτταρικός πληθυσμός μικρού μεγέθους λεμφοκύτταρα.
Ποσοστό διήθησης: 95 % του κυτταρικού πληθυσμού.
Πρότυπο ανάπτυξης: Κυρίως διάμεσο.



Λεμφοκυτταρικός πληθυσμός μικρού μεγέθους λεμφοκύτταρα.
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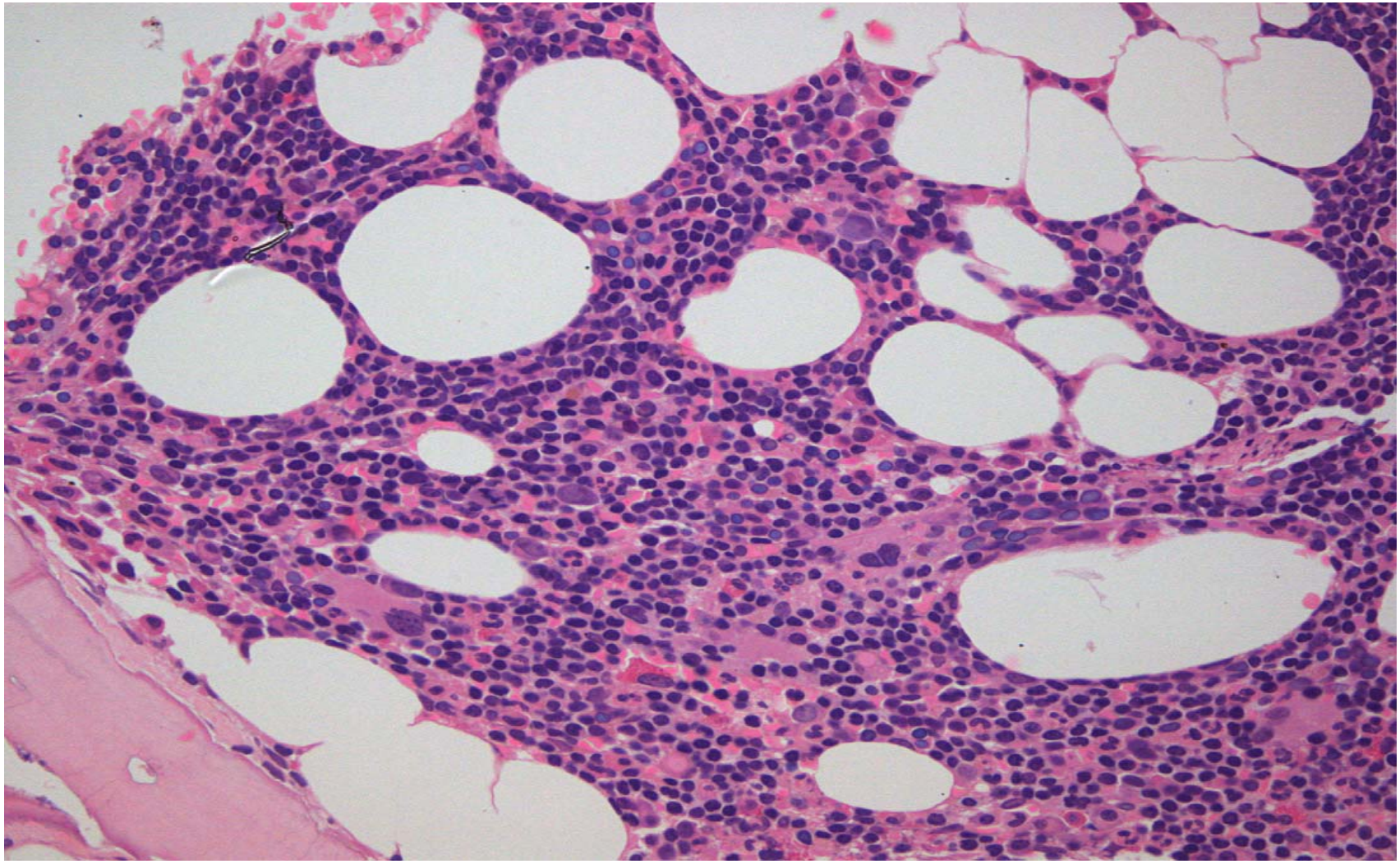
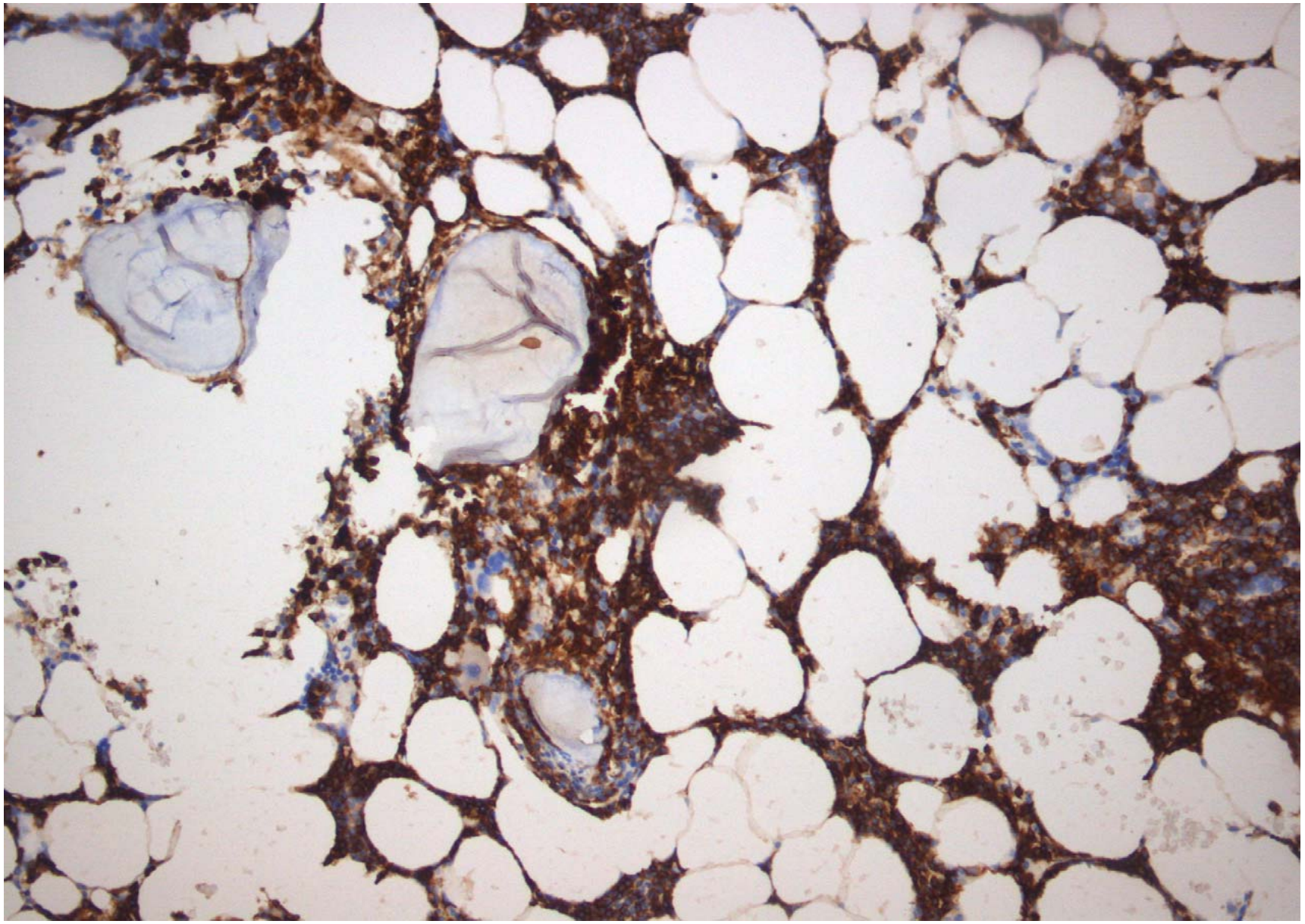
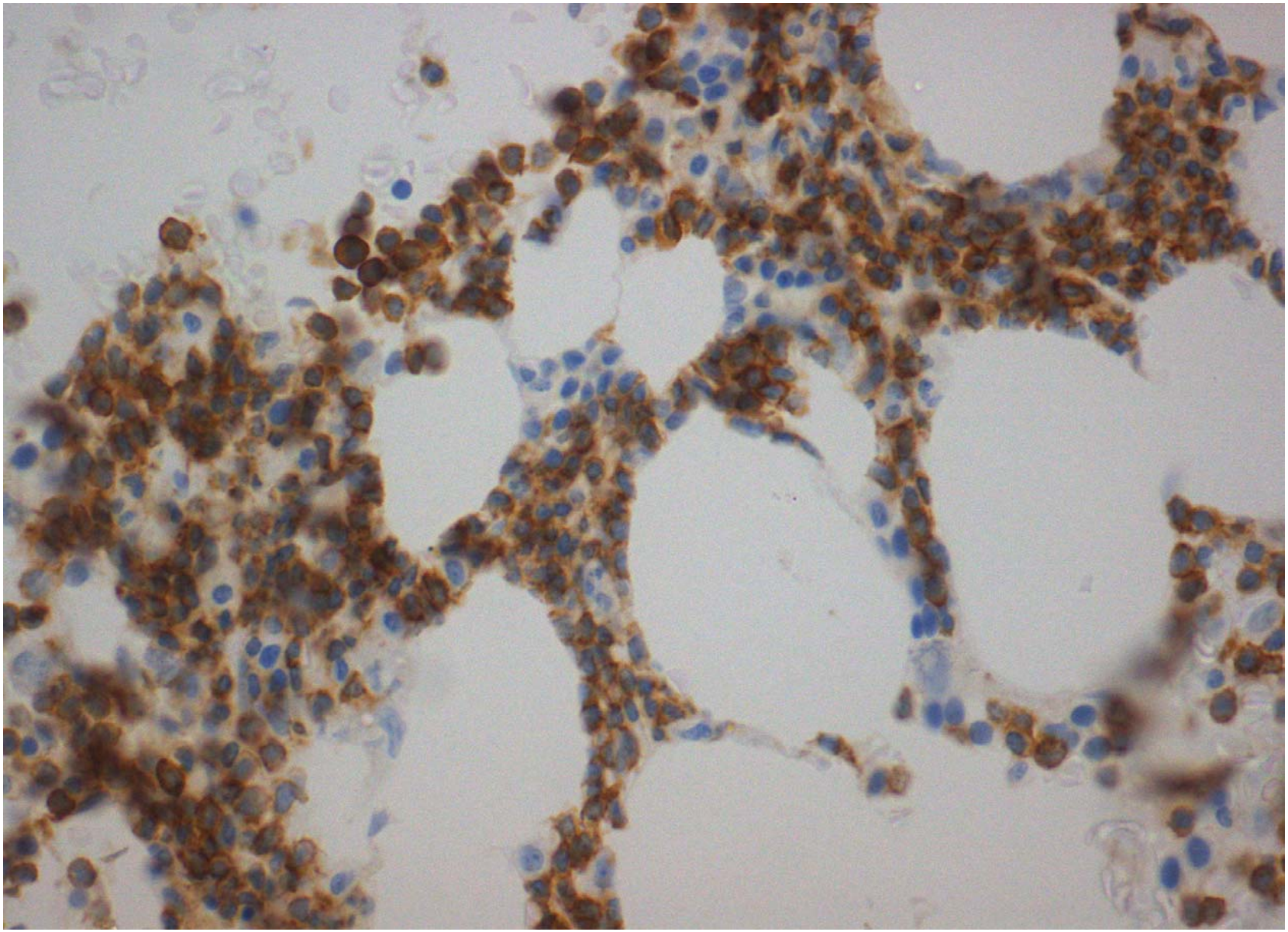


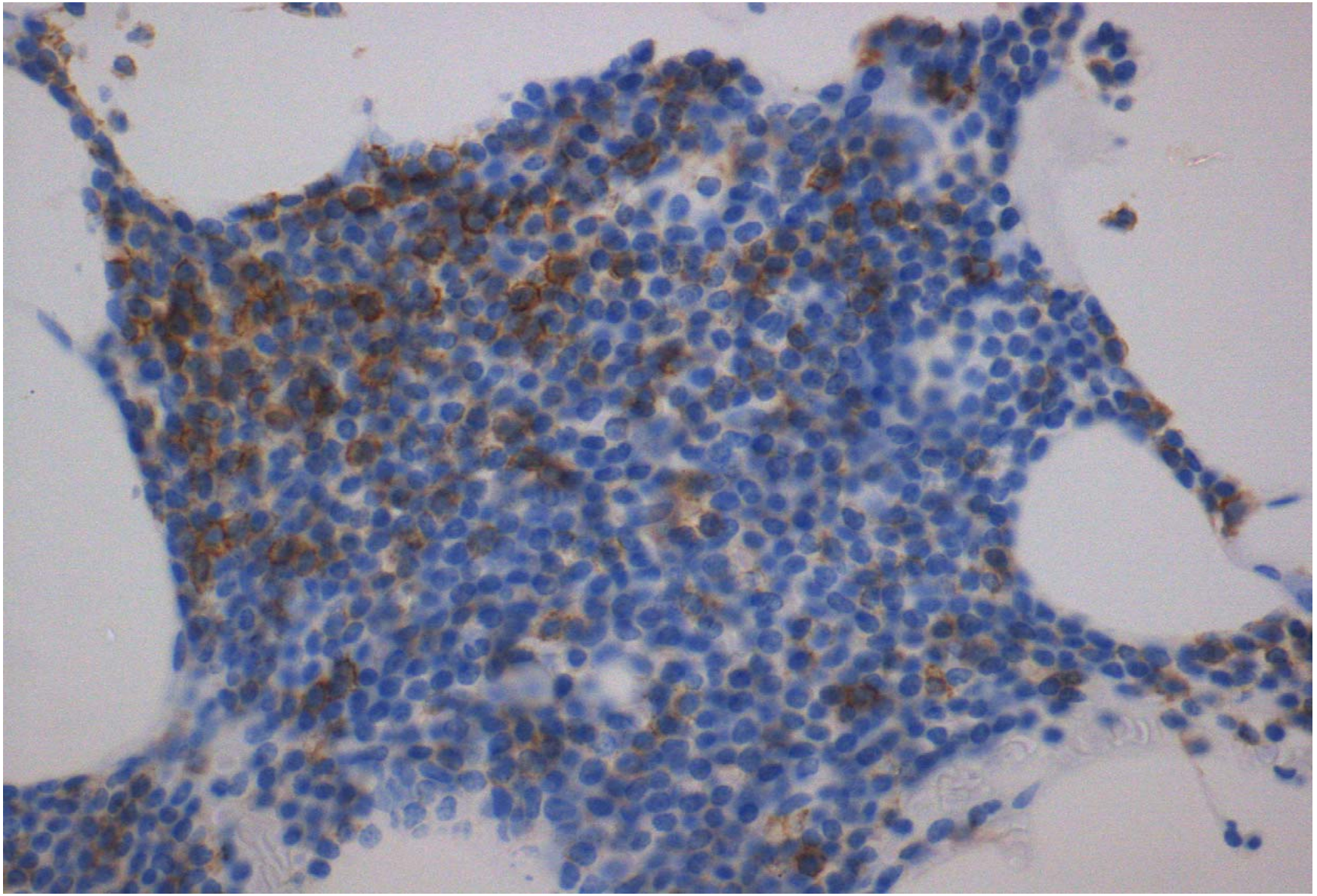
Μικρού μεγέθους λεμφοκύτταρα και πλασματοκύτταρα.
Ποσοστό διήθησης: 95 % του κυτταρικού πληθυσμού.
Πρότυπο ανάπτυξης: Κυρίως διάμεσο.



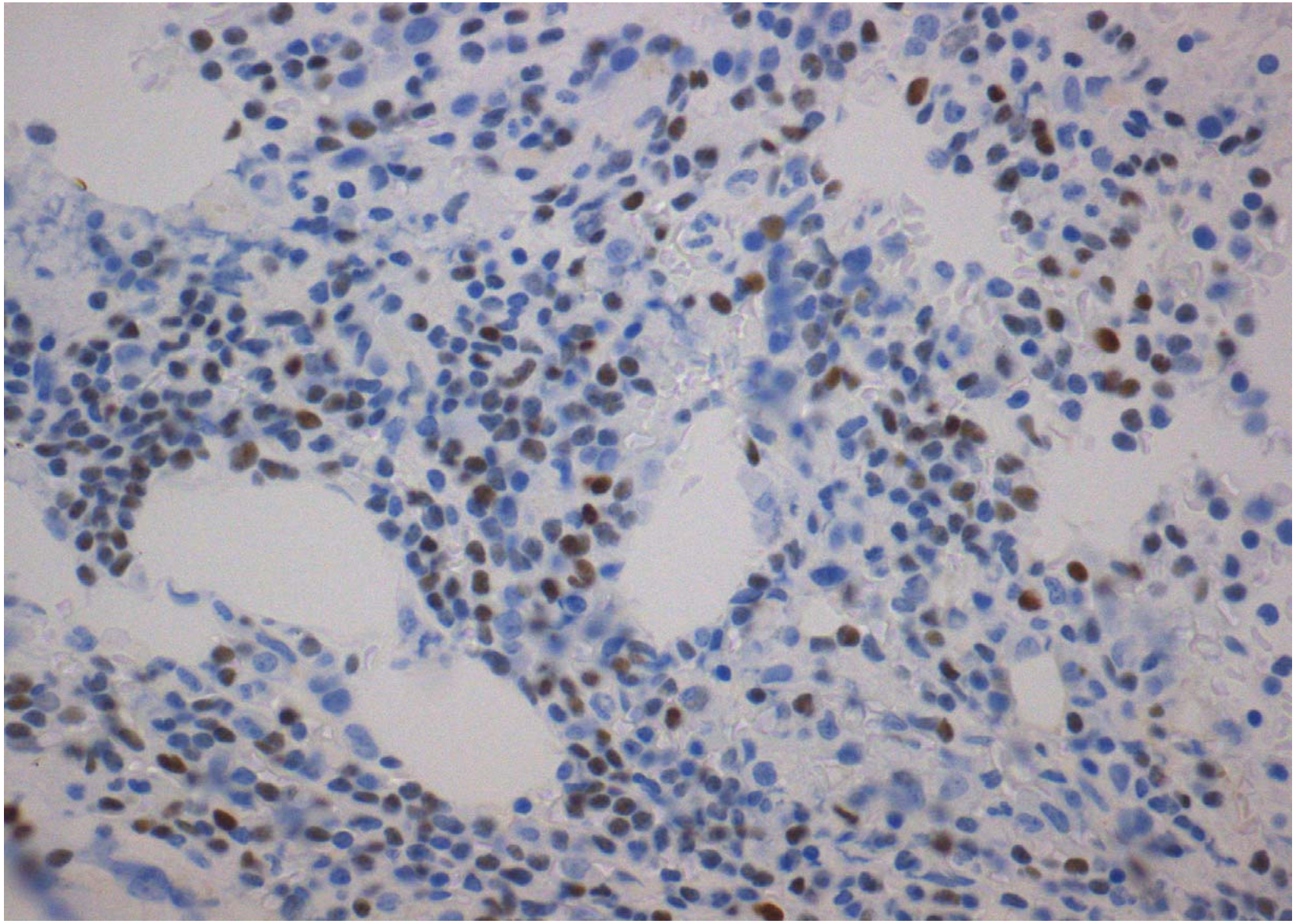
Ανοσοέκφραση μέτριας έως έντονης έντασης αντιγόνου CD20



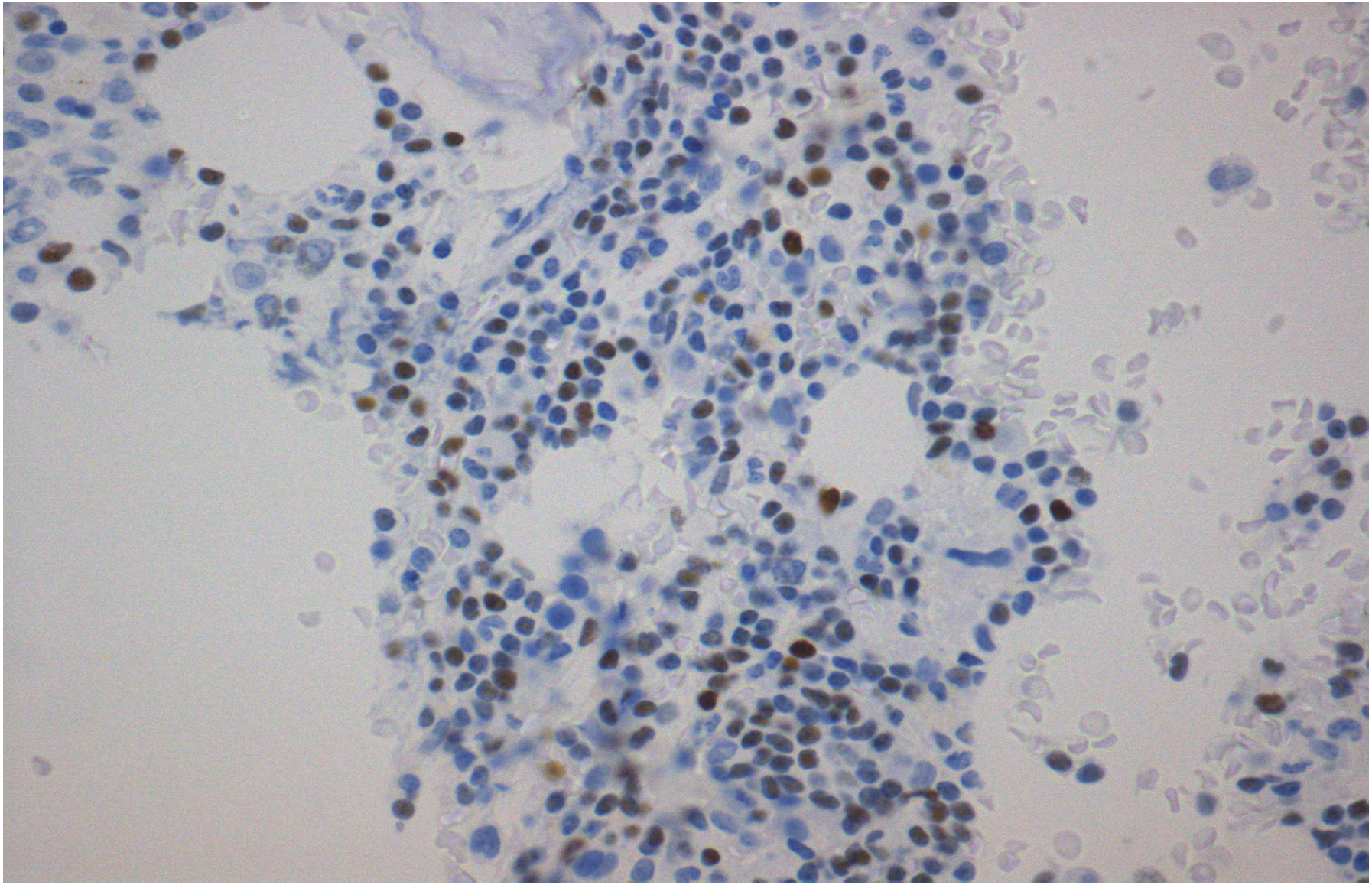
Ανοσοέκφραση μέτριας έως έντονης έντασης αντιγόνου CD5



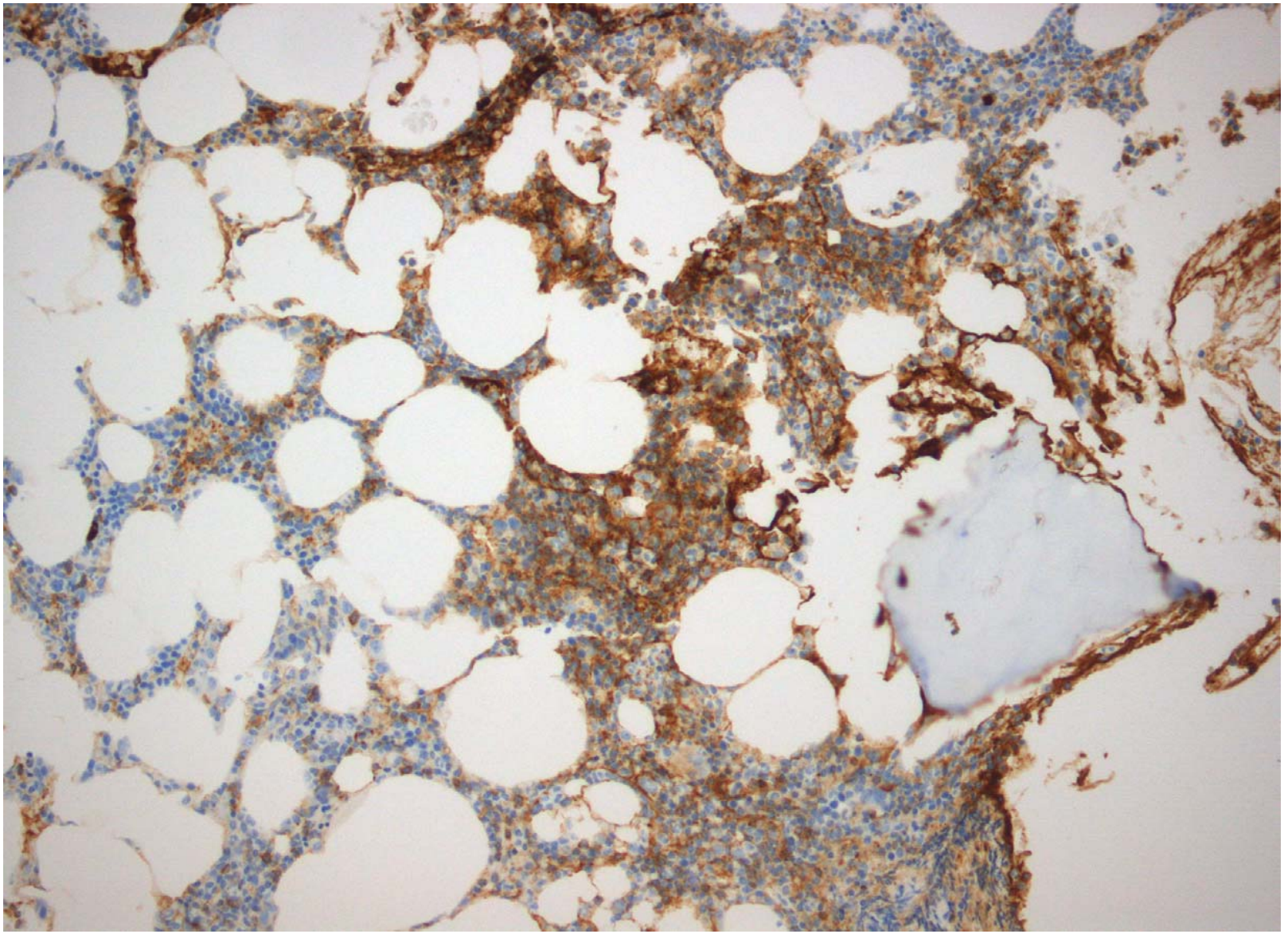
Συνέκφραση CD23 αντιγόνου



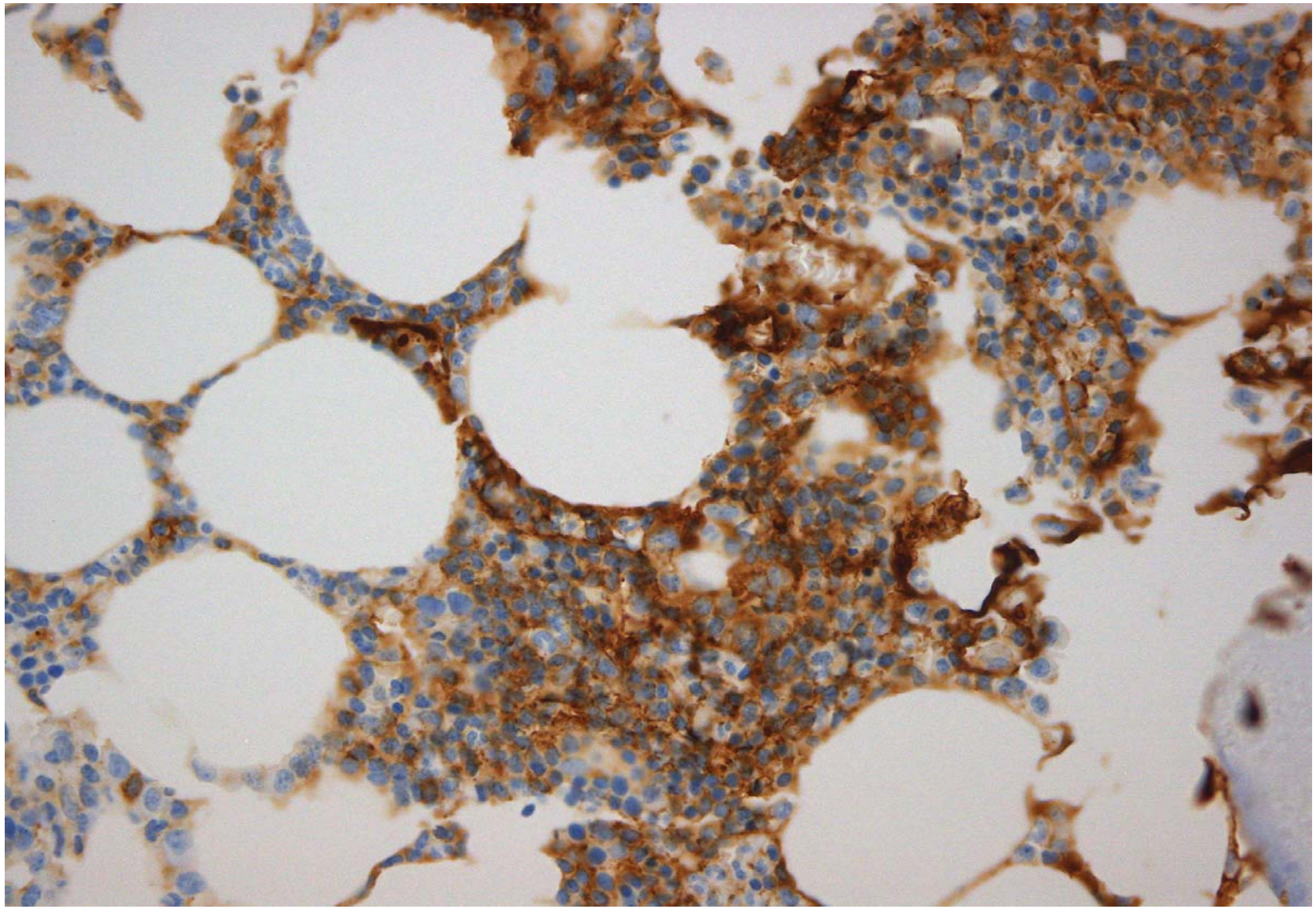
Πυρηνική έκφραση LEF-1 +(100% των κυττάρων)



LEF-1 +(100% των κυττάρων). Έκφραση στο σύνολο σχεδόν των περιπτώσεων CLL/SLL.



Ανοσοσφαιρίνες επιφανείας / κυτταροπλάσματος IgM



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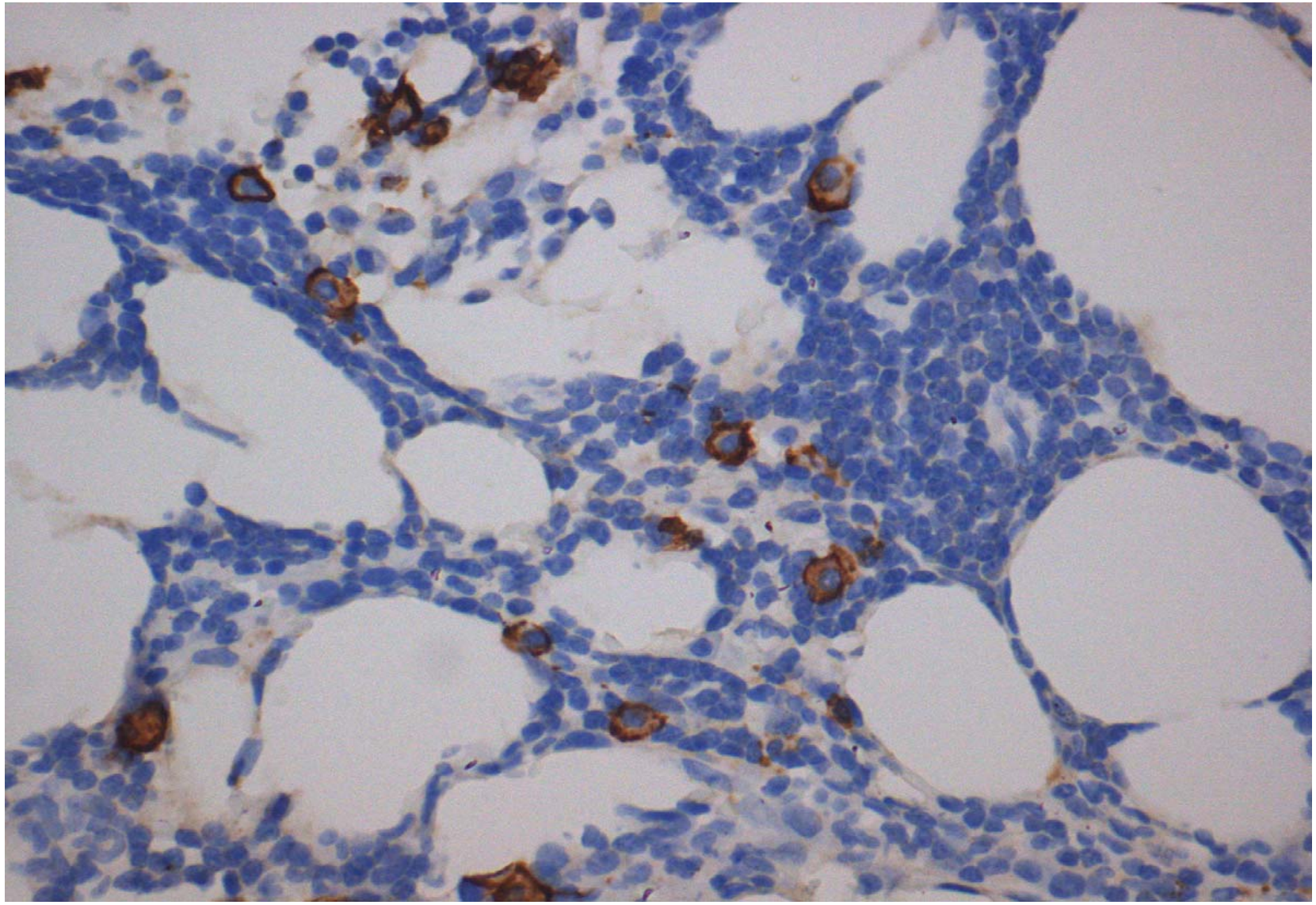
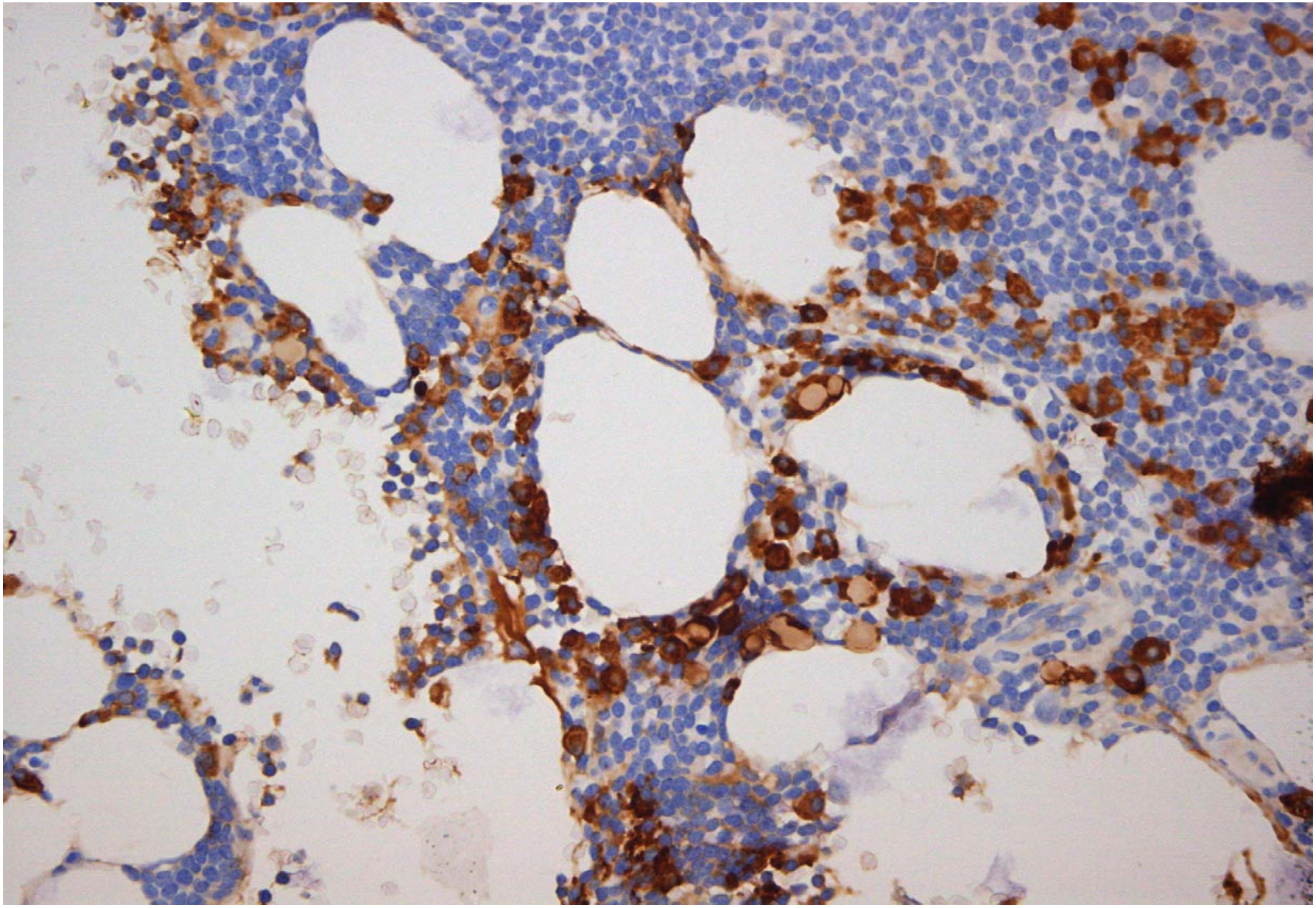
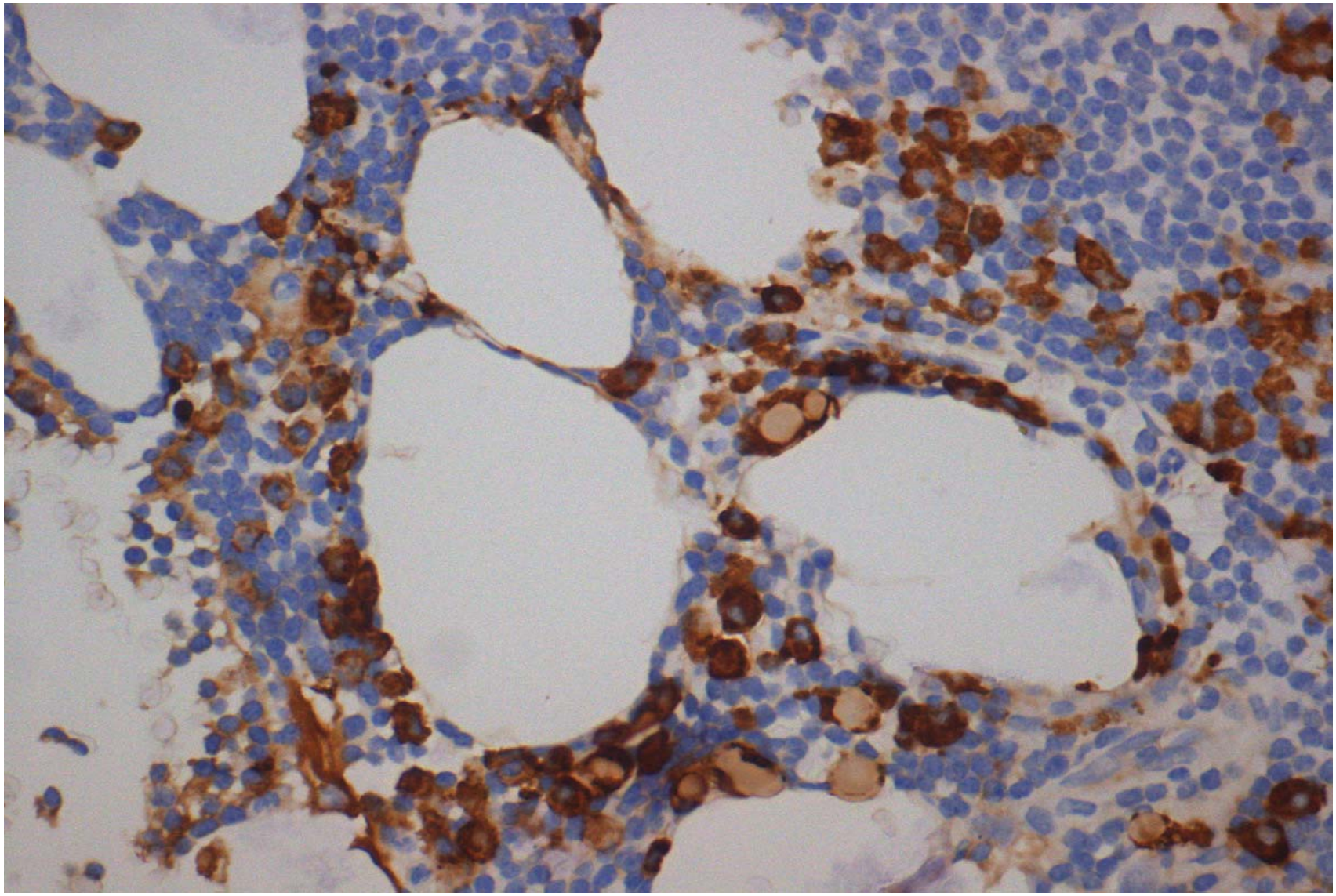


Ώριμα πλασματοκύτταρα CD138 (+) σε ποσοστό ~ 8% του κυτταρικού πληθυσμού. Απουσία έκφρασης CD56 & Cyclin D1.



Μονοκλωνική παραγωγή λ ελαφράς αλύσσου



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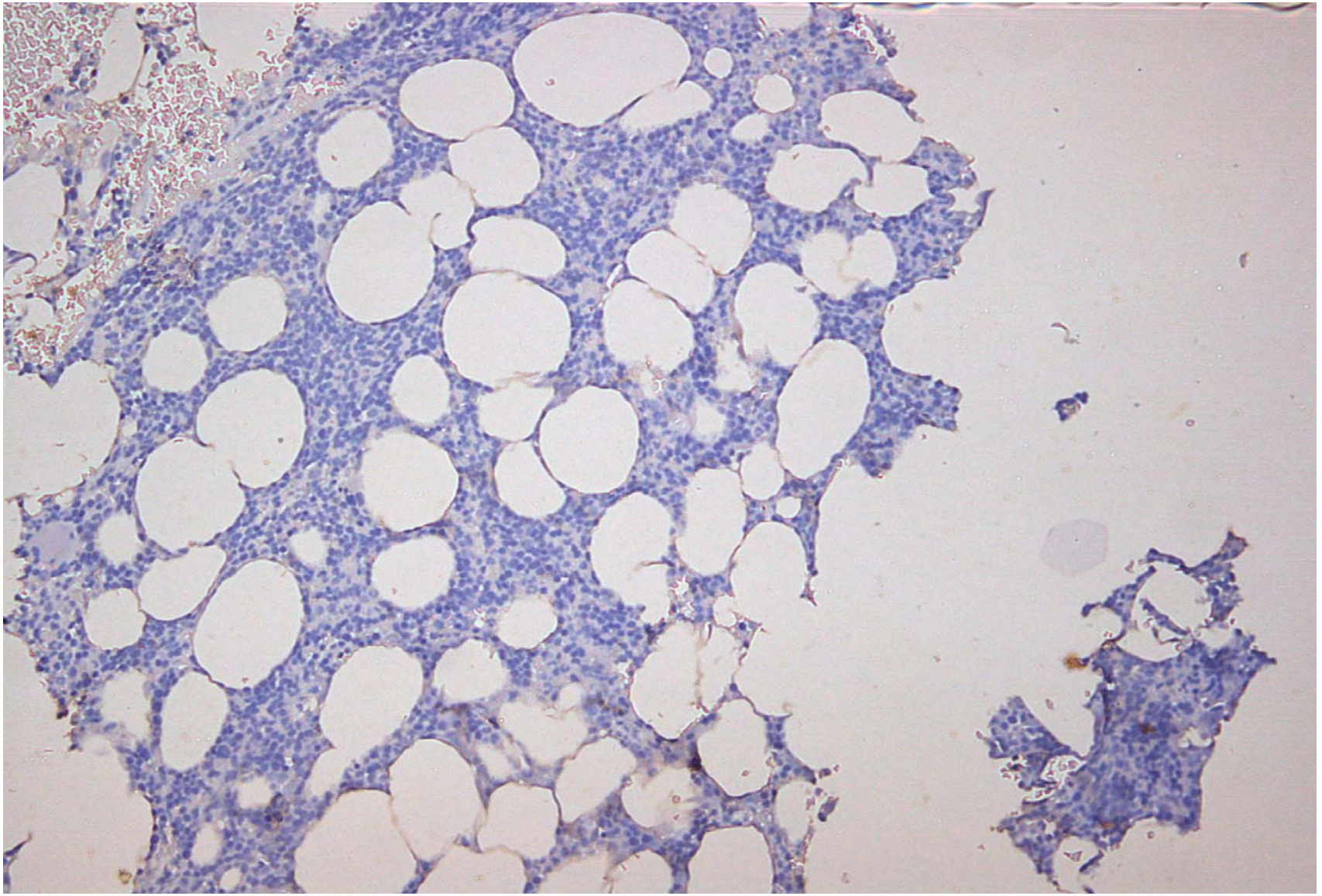
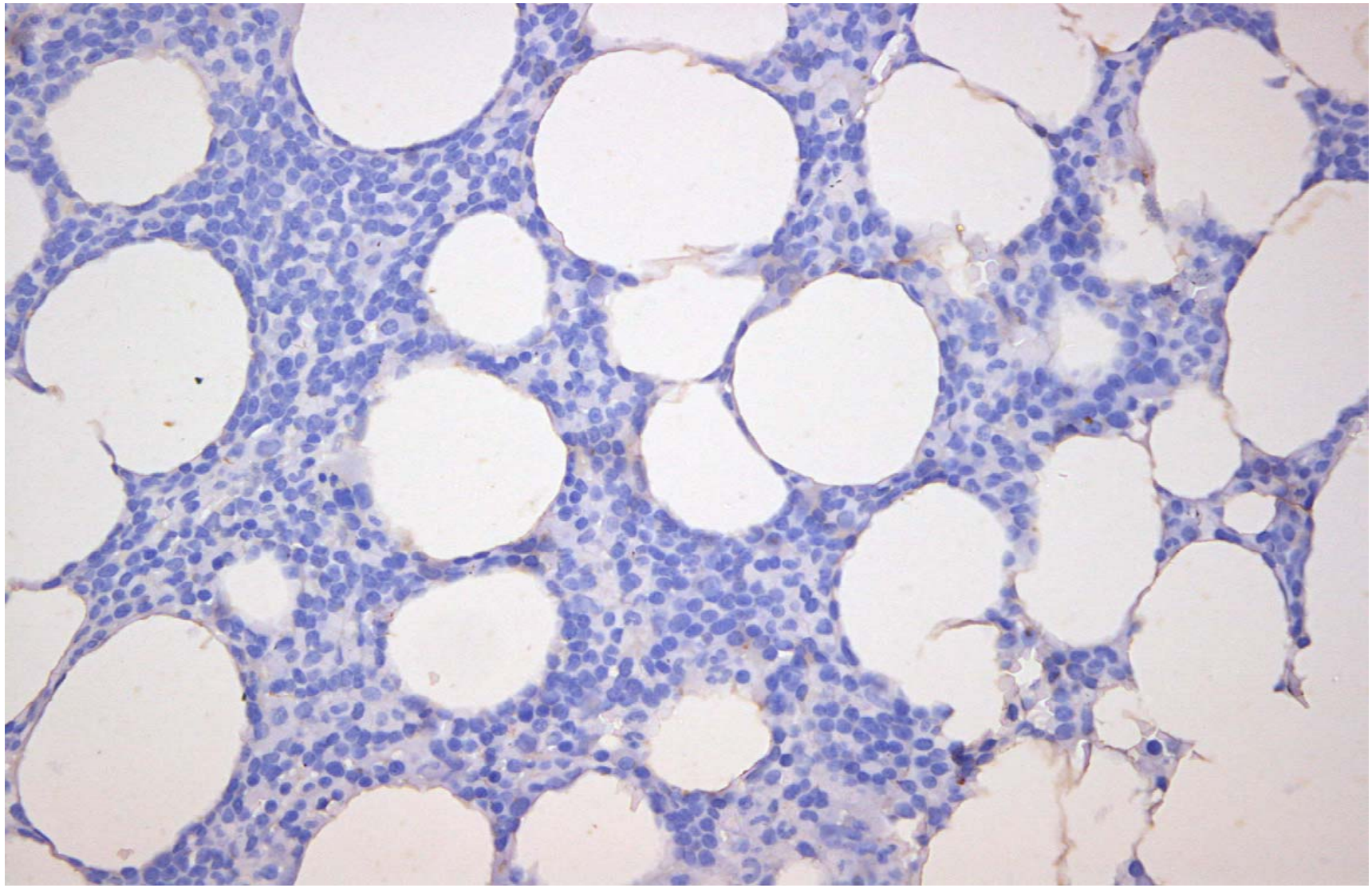


Απουσία έκφρασης κ ελαφράς αλύσσου



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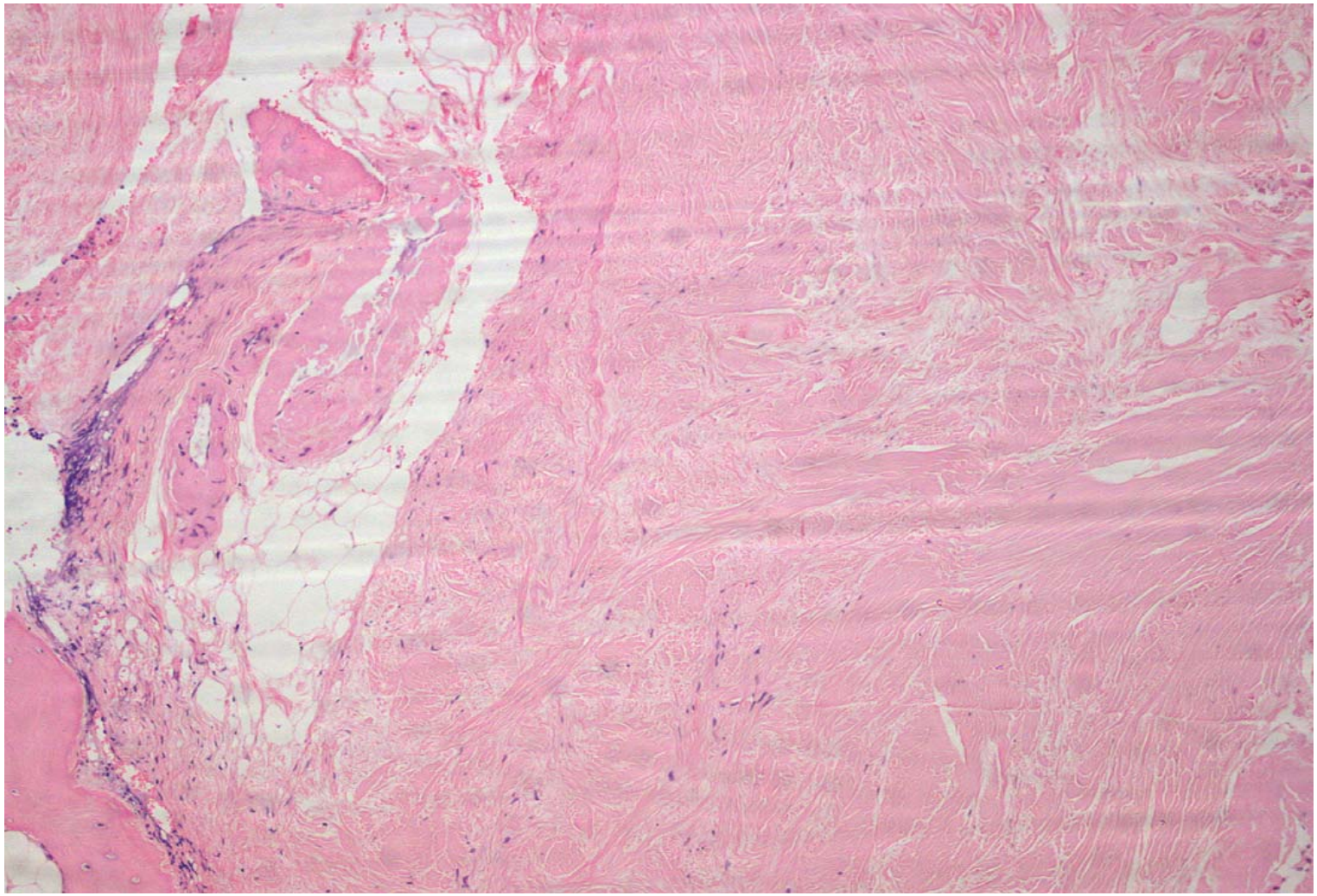
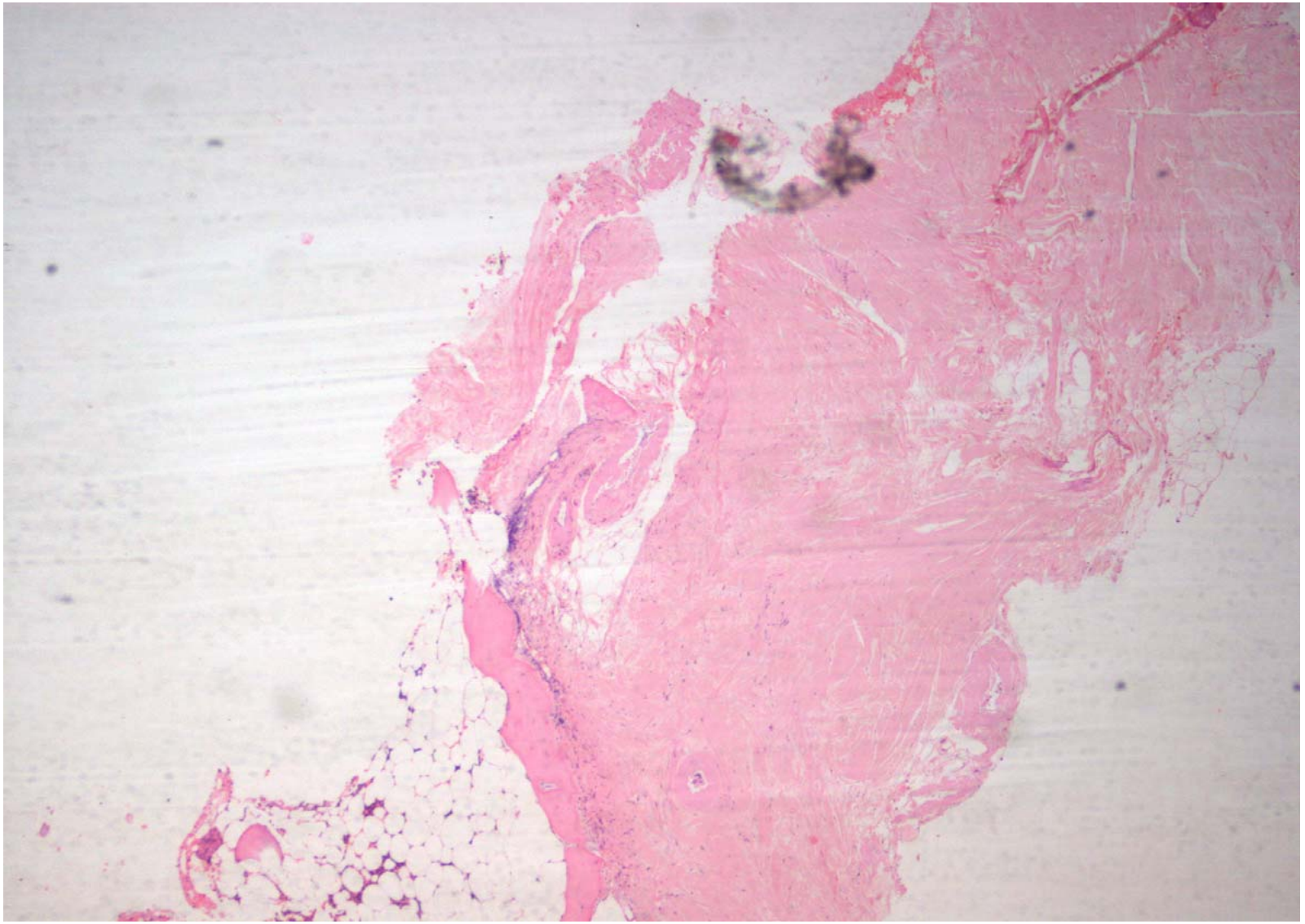
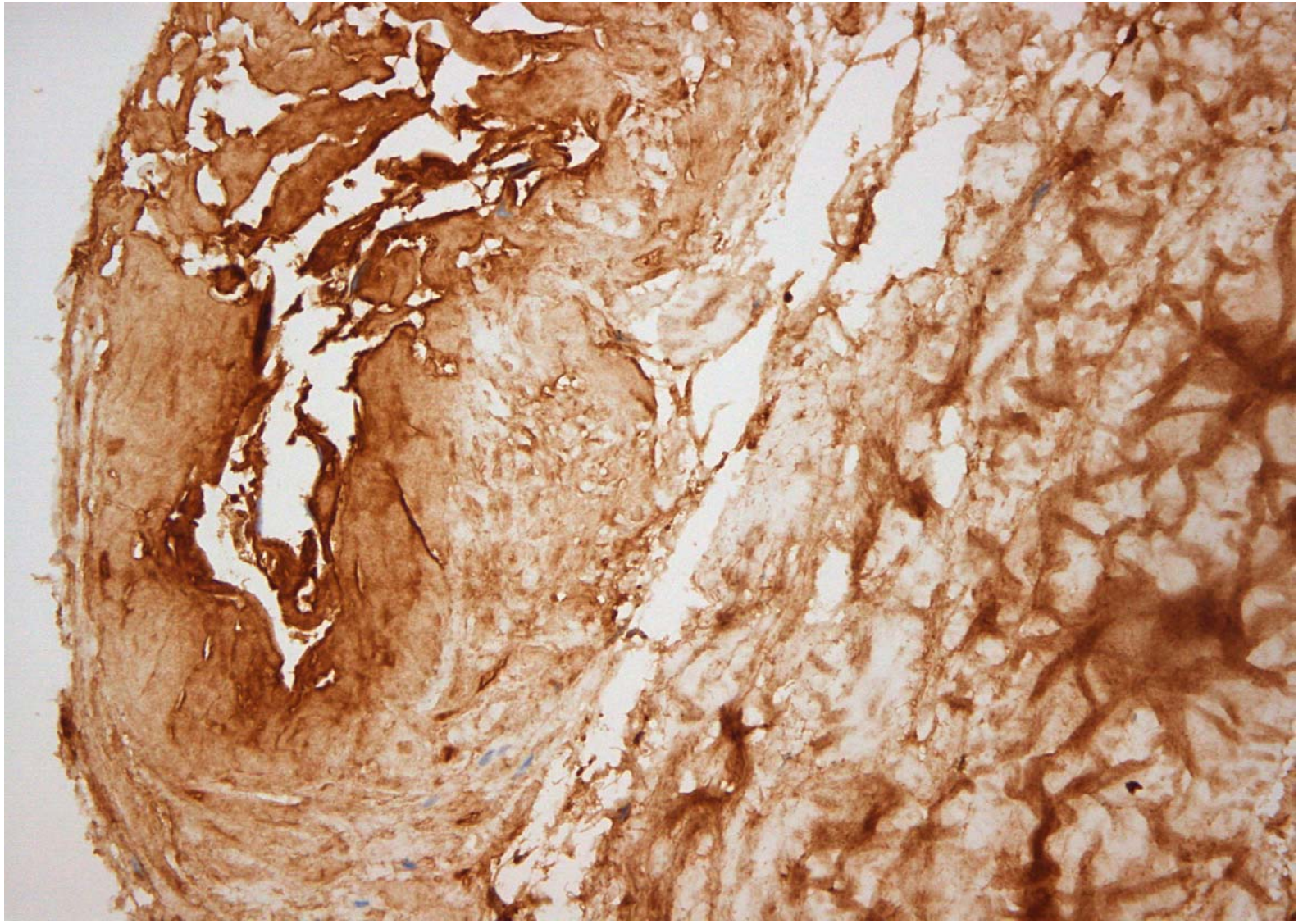


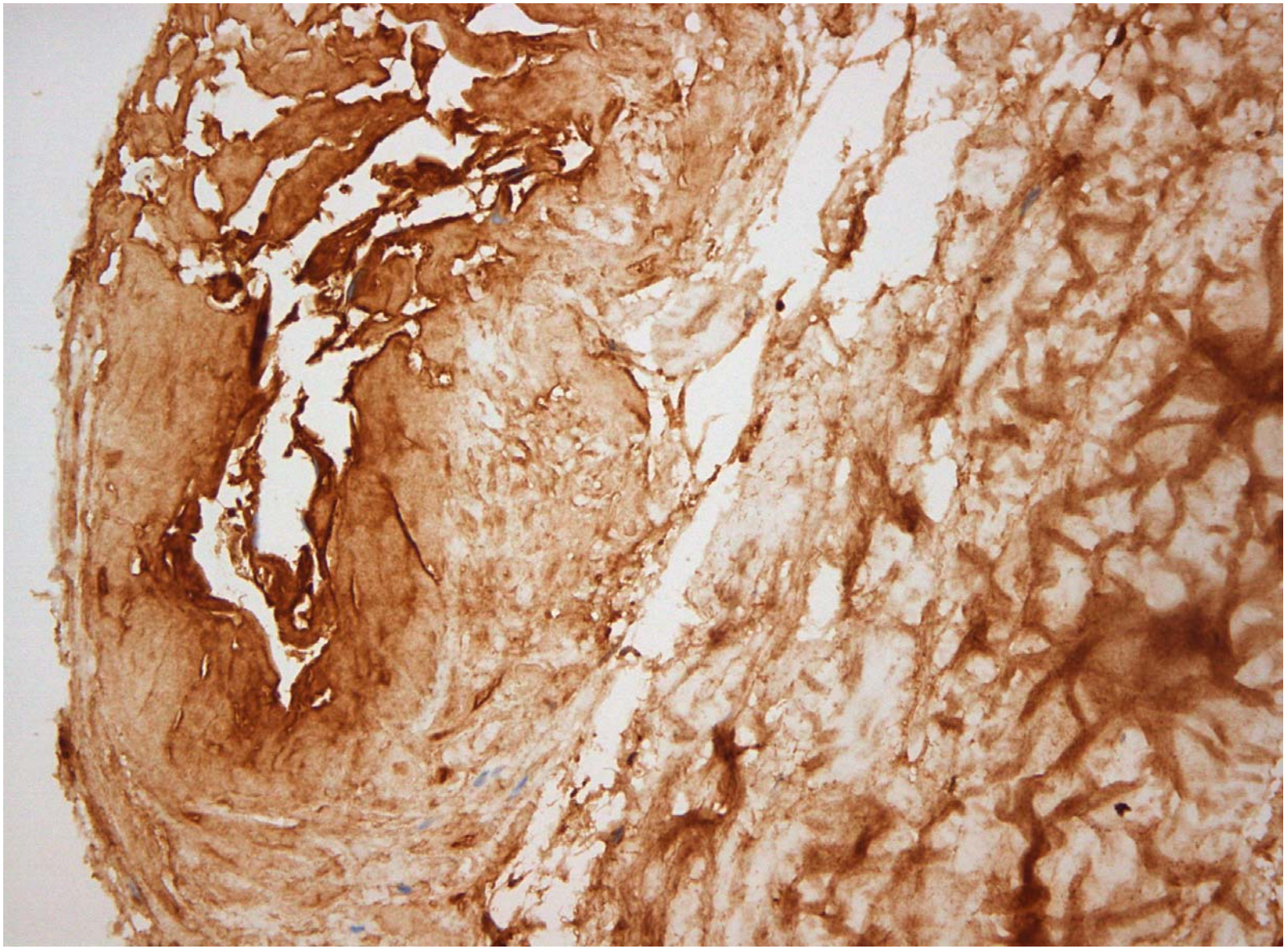
Εναποθέσεις άμορφης, ελαφρά ηωσινόφιλης ουσίας στο τοίχωμα αγγείων



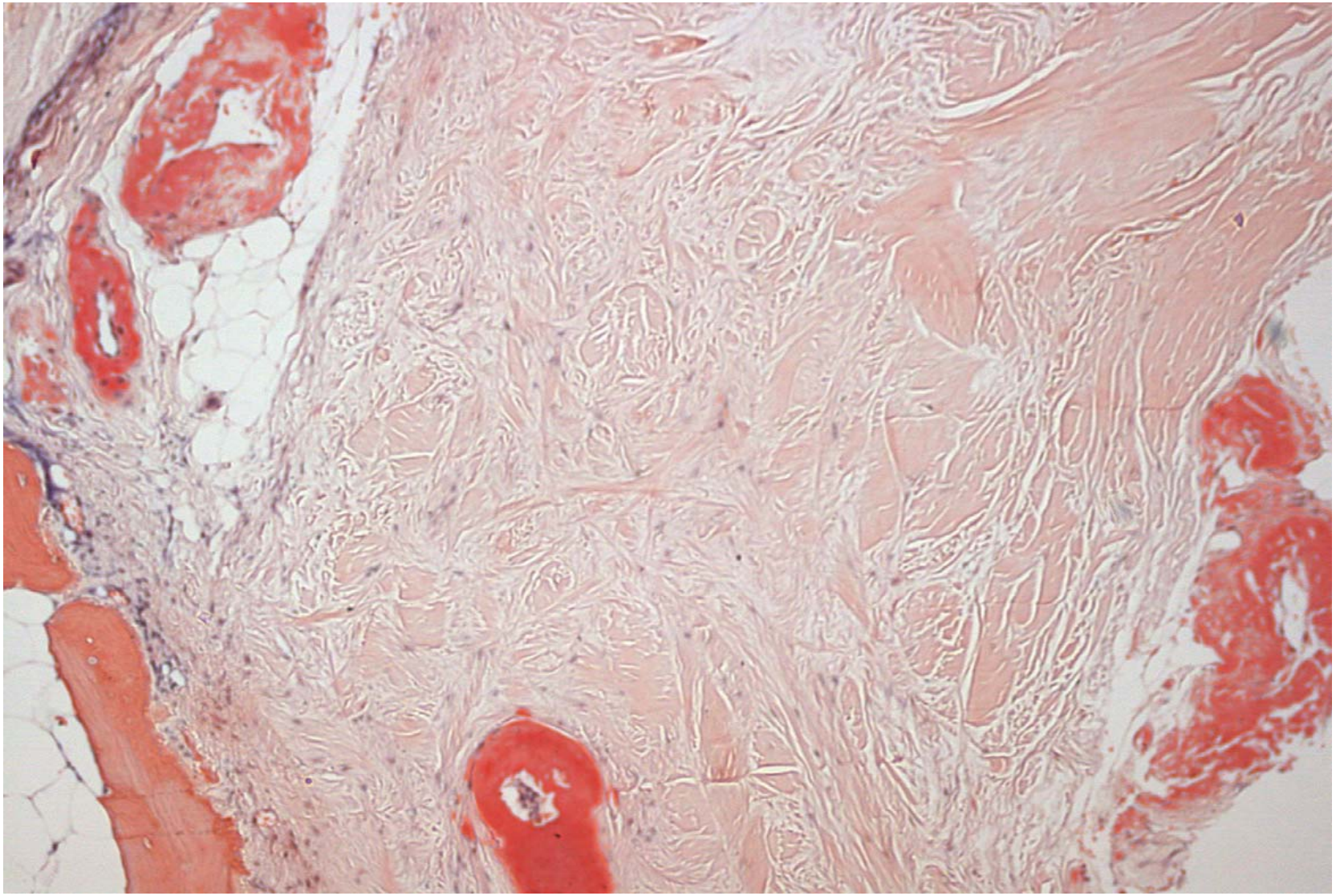
Εναποθέσεις άμορφης ήπια ηωσινόφιλης ουσίας στο τοίχωμα αγγείων.



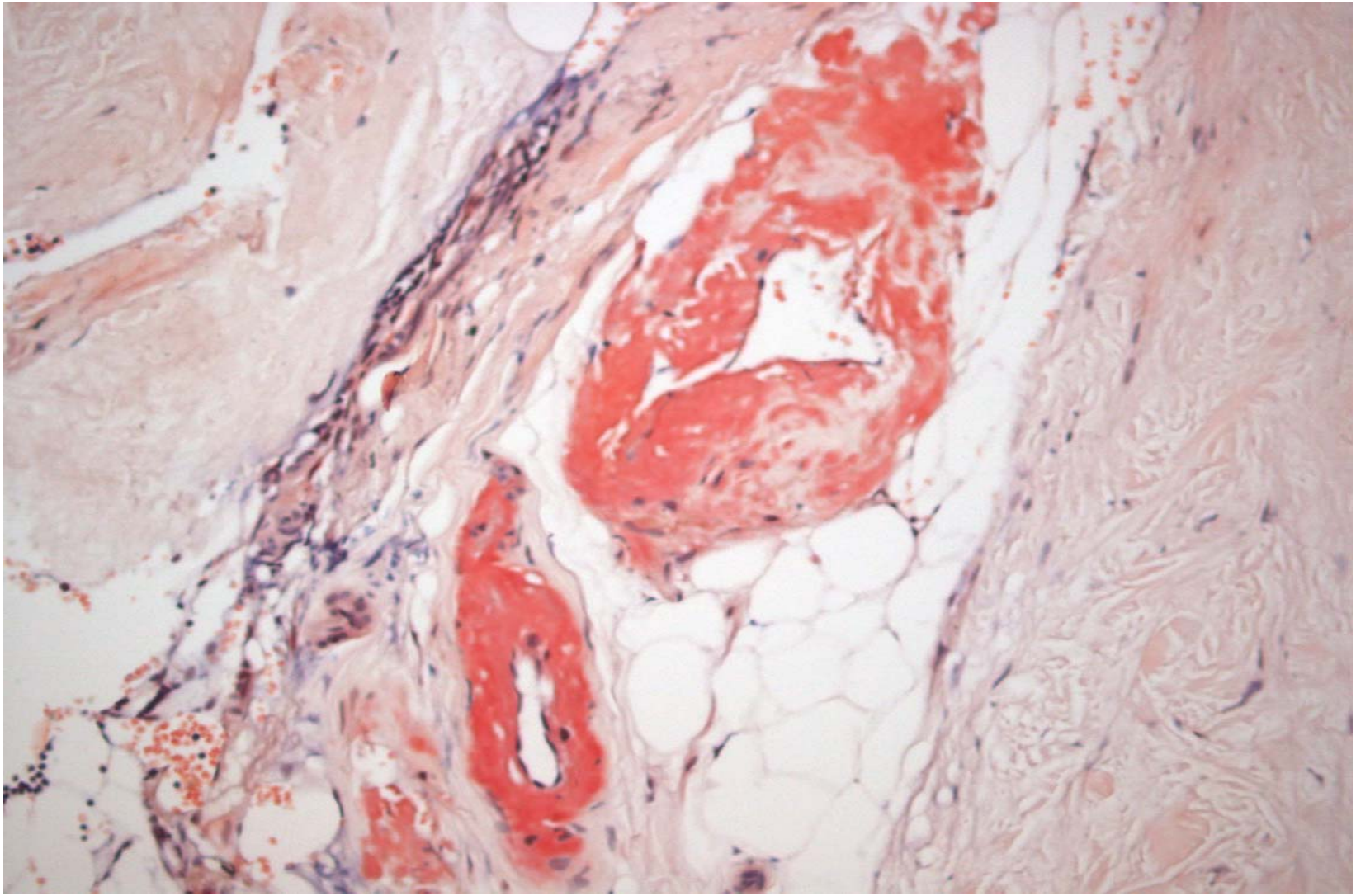
Εναποθέσεις λ ελαφράς αλύσσου στο τοίχωμα αγγείων



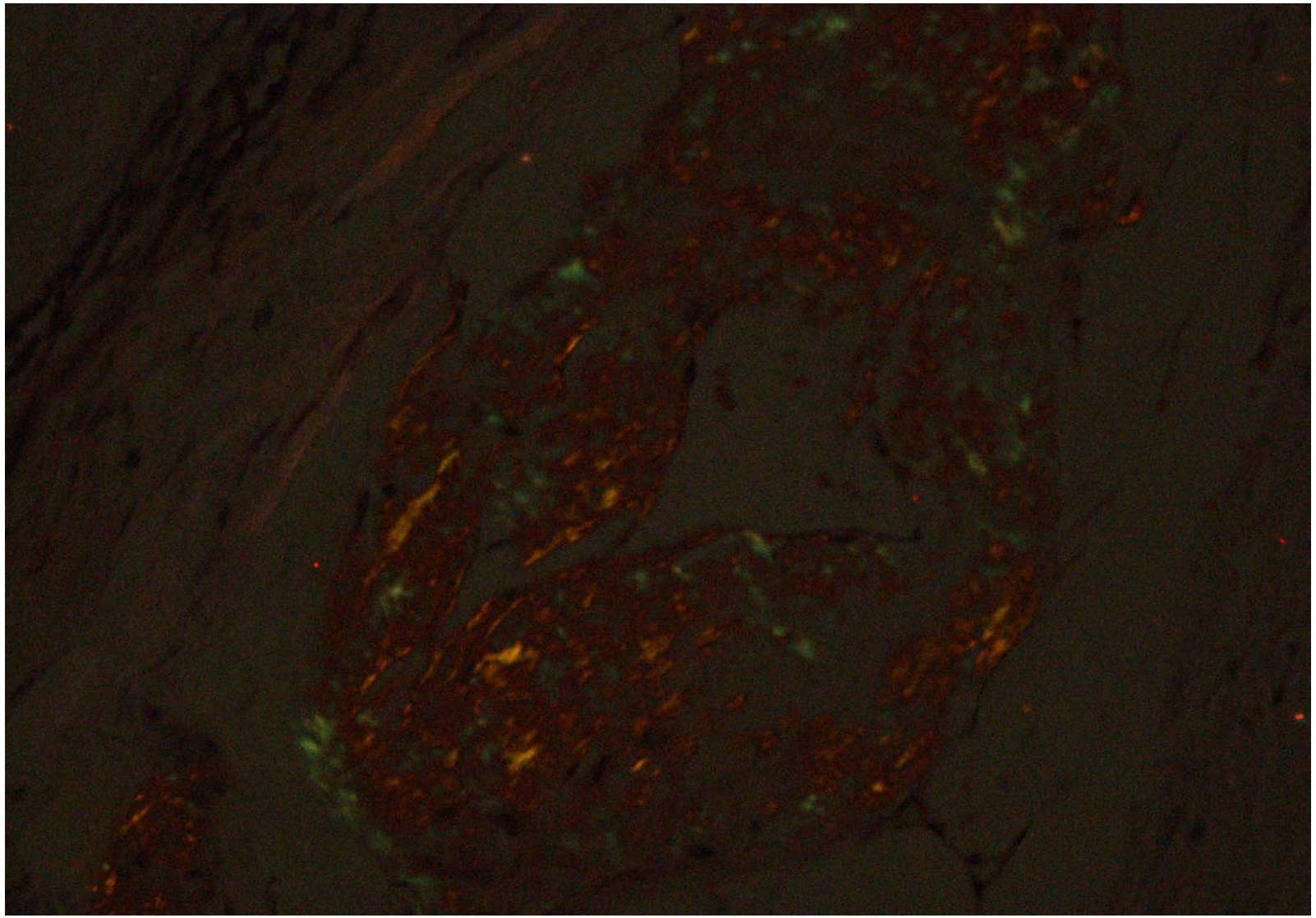
Εναποθέσεις λ ελαφρών αλύσσεων στο τοίχωμα αγγείου & περιαγγειακά



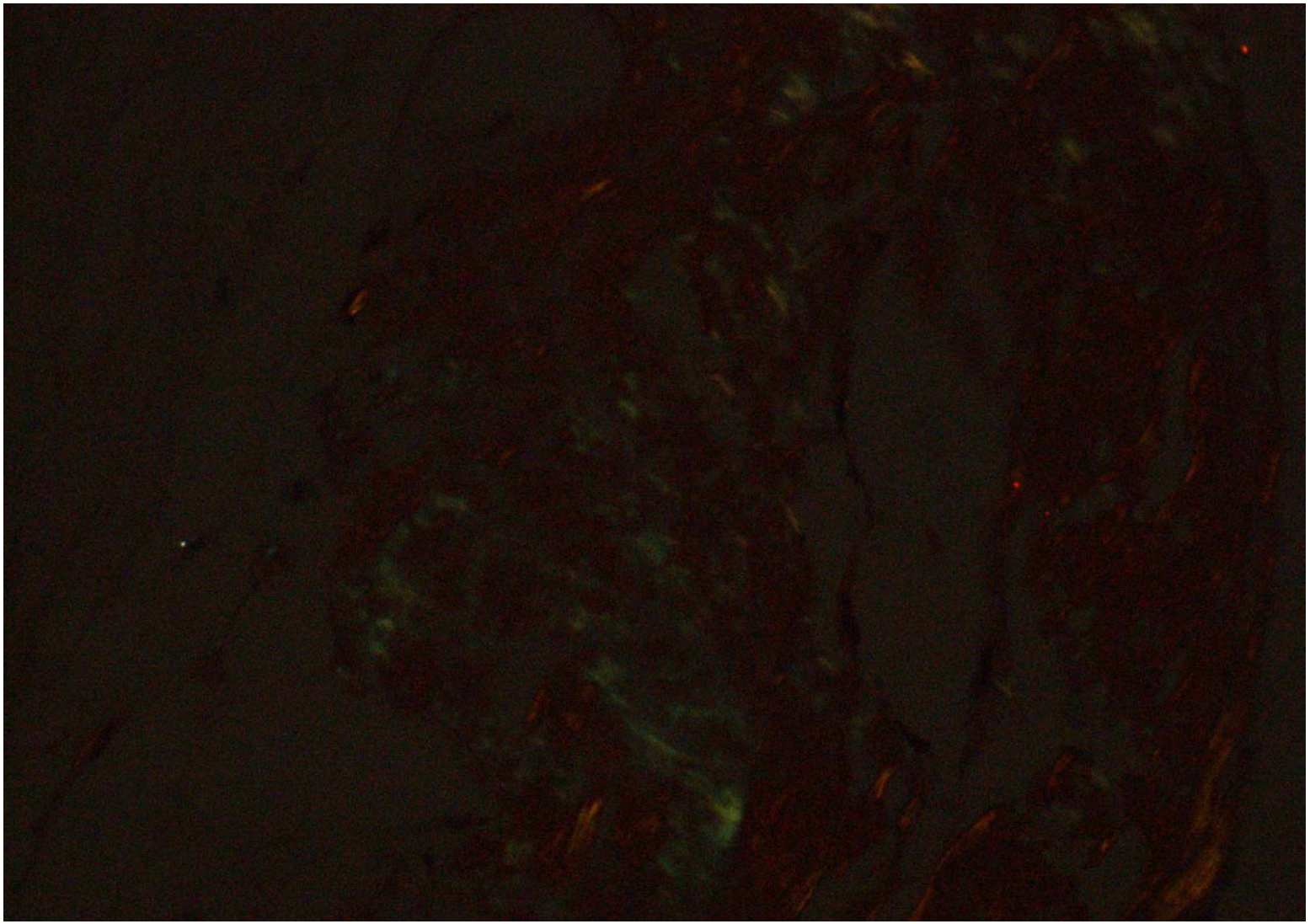
AL αμυλοείδωση: Salmon pink χρώση του αμυλοειδούς με την χρώση Congo red



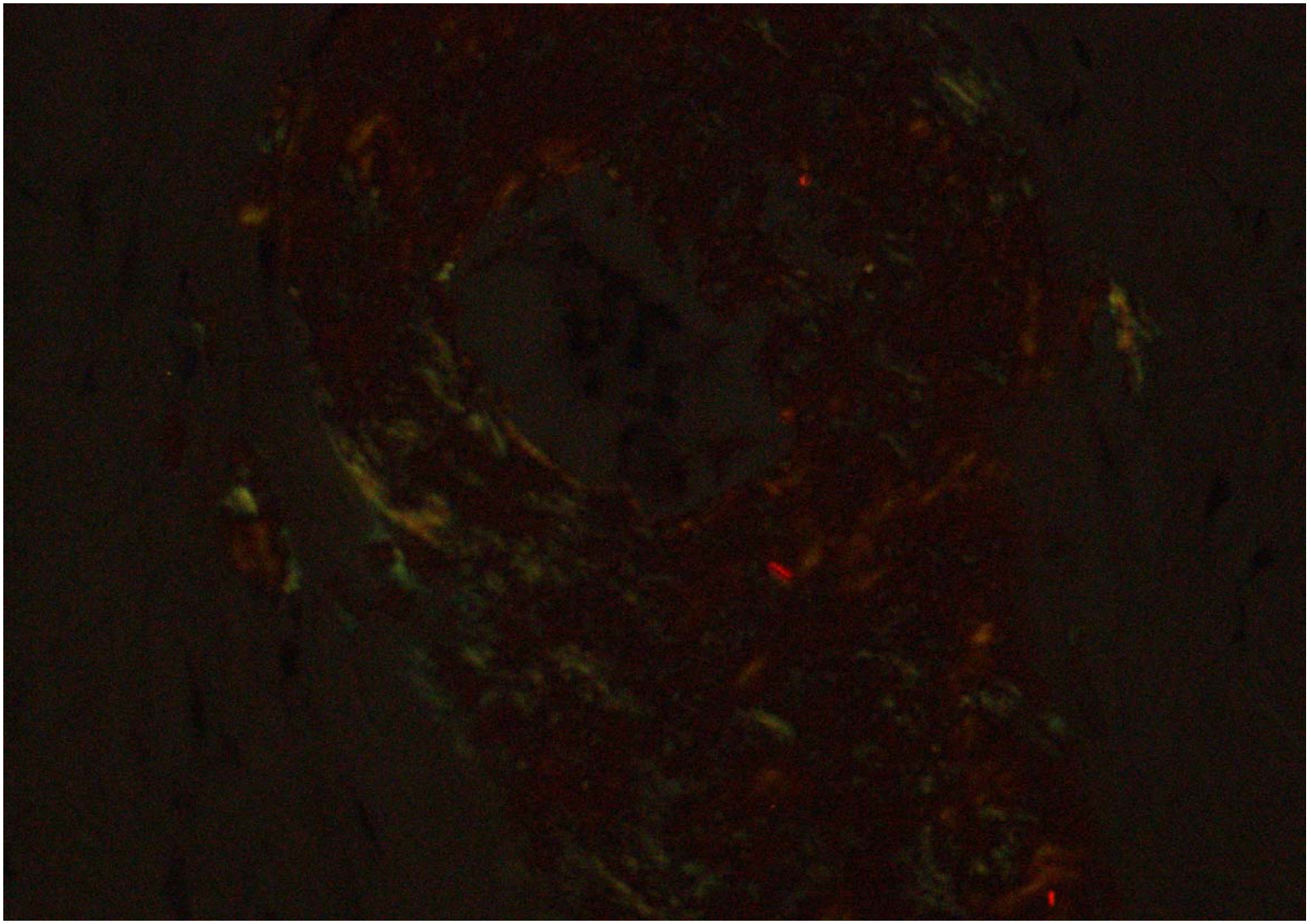
Congo red: Εναποθέσεις αμυλοειδούς



Apple green birefringence / διχρωϊσμός στο πολωτικό φώς



Apple green birefringence / διχρωϊσμός στο πολωτικό φώς



Apple green birefringence / διχρωϊσμός στο πολωτικό φώς

1. Διήθηση αιμοποιητικού μυελού από μη Hodgkin λέμφωμα Β κυτταρικής προέλευσης με ανοσομορφολογικούς χαρακτήρες συμβατούς με λεμφοκυτταρικό λέμφωμα από μικρά λεμφοκύτταρα/ Β χρόνια λεμφοκυτταρική λευχαιμία –ταξινόμηση κατά WHO 2017 CLL/SLL ICD0-code 9823/3

2. Πλασματοκυτταρική μονοκλωνική παρουσία με παραγωγή λ ελαφράς αλύσσου.

3. Συστηματική αμυλοείδωση.

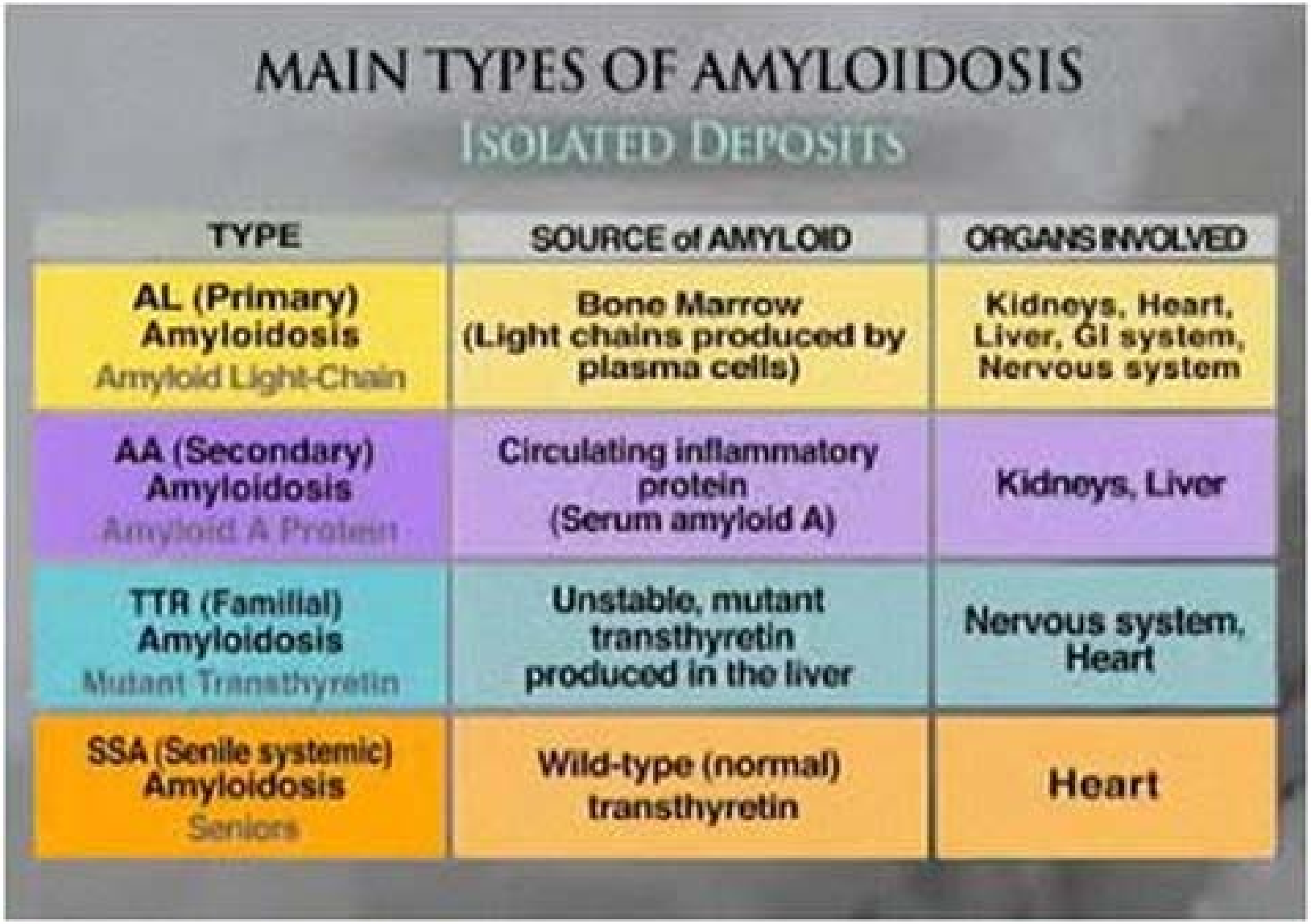
Σχόλια: Συζητούνται τα ενδεχόμενα :

1. Β χρόνια λεμφοκυτταρική λευχαιμία με πλασματοκυτταρική διαφοροποίηση και συνοδό αμυλοείδωση εάν αποδειχθεί η παραγωγή λ ελαφράς αλύσσου από τον λεμφοκυτταρικό πληθυσμό με την μέθοδο της κυτταρομετρίας ροής,

2. Συνύπαρξη Β χρόνιας λεμφοκυτταρικής λευχαιμίας και πλασματοκυτταρικής δυσκρασίας /αμυλοείδωση από διαφορετικούς κλώνους.

TABLE 22.1 Systemic amyloidoses in humans: amyloid fibril proteins and their precursors

Amyloid protein	Precursor	Systemic (S) or localized (L)	Syndrome
AL/AH	Immunoglobulin light/heavy chain	S, L	Sporadic: primary, myeloma associated
AA	Serum AA protein	S, ?L	Sporadic: secondary, reactive; familial
ATTR	Transthyretin	S, ?L	Familial, sporadic—senile systemic
AFib	Fibrinogen A α-chain	S	Familial
AApoAI, II, IV	Apolipoprotein AI, AII, AIV	S, L	Familial, sporadic (aging)
AGel	Gelsolin	S	Familial
ALys	Lysozyme	S	Familial
ACys	Cystatin C	S	Familial
ALect2	Leukocyte chemotactic factor 2	S	Familial?
$A\beta_2M$	β_2-Microglobulin	S, ?L	Dialysis associated

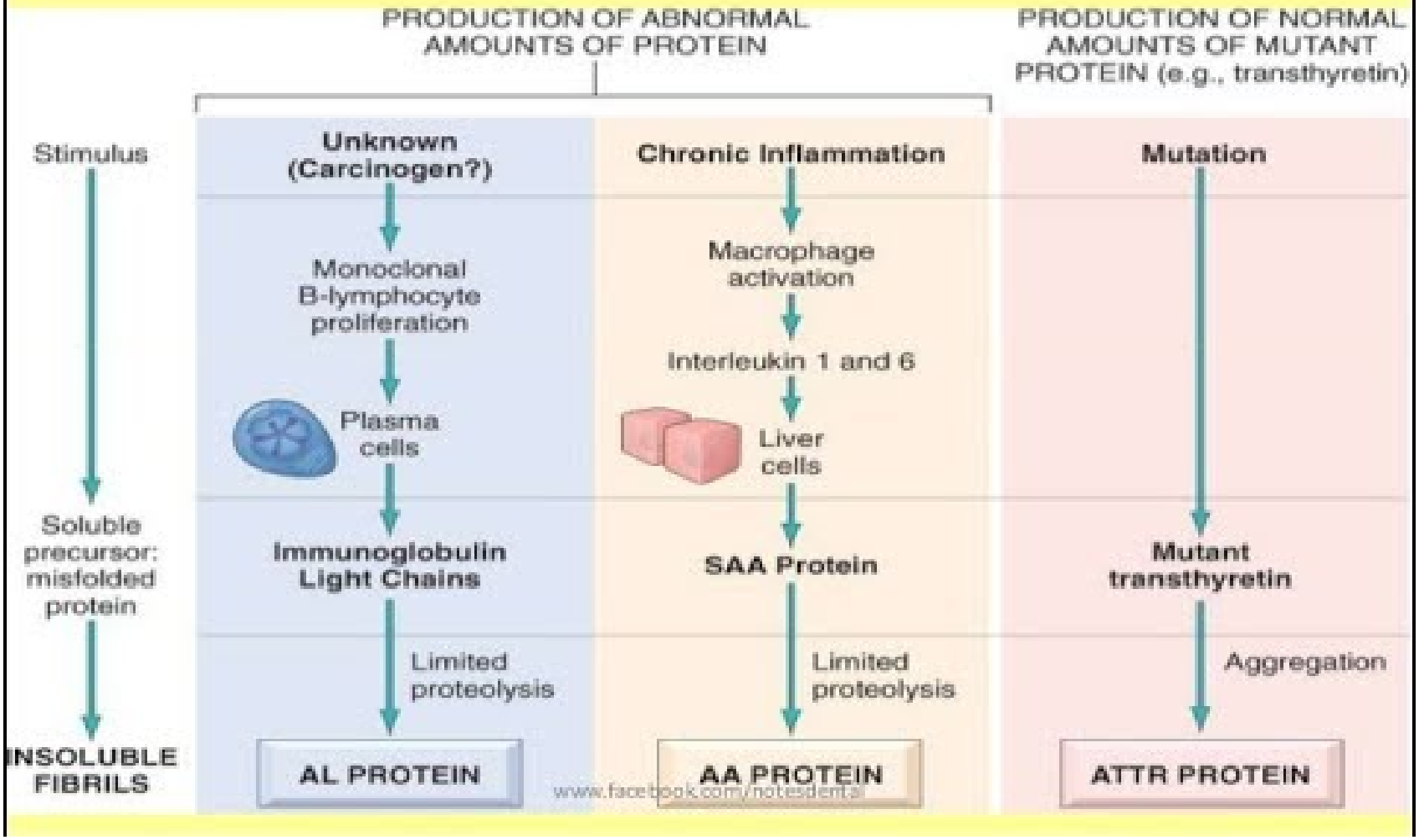

MAIN TYPES OF AMYLOIDOSIS
ISOLATED DEPOSITS
TYPE
SOURCE of AMYLOID
ORGANS INVOLVED
AL (Primary) Amyloidosis
Amyloid Light-Chain
Bone Marrow (Light chains produced by plasma cells)
Kidneys, Heart, Liver, GI system, Nervous system
AA (Secondary) Amyloidosis
Amyloid A Protein
Circulating inflammatory protein (Serum amyloid A)
Kidneys, Liver
TTR (Familial) Amyloidosis
Mutant Transthyretin
Unstable, mutant transthyretin produced in the liver
Nervous system, Heart
SSA (Senile systemic) Amyloidosis
Seniors
Wild-type (normal) transthyretin
Heart

CLASSIFICATION OF AMYLOIDOSIS

Category	Associated Disease	Biochemical Type	Organs Commonly Involved
A. SYSTEMIC (GENERALISED) AMYLOIDOSIS			
1. *Primary*	Plasma cell dyscrasias	AL type	Heart, bowel, skin, nerves, kidney
2. *Secondary (Reactive)*	Chronic inflammation, cancers	AA type	Liver, spleen, kidneys, adrenals
3. *Haemodialysis-associated*	Chronic renal failure	$A\beta_2M$	Synovium, joints, tendon sheaths
4. *Heredofamilial*			
i. *Hereditary polyneuropathies*	—	ATTR	Peripheral and autonomic nerves, heart
ii. *Familial Mediterranean fever*	—	AA type	Liver, spleen, kidneys, adrenals
iii. *Rare hereditary forms*	—	AApoAI, AGel ALys, AFib, ACys	Systemic amyloidosis
B. LOCALISED AMYLOIDOSIS			
1. *Senile cardiac*	Senility	ATTR	Heart
2. *Senile cerebral*	Alzheimer's, transmissible encephalopathy	Aβ, APrP	Cerebral vessels, plaques, neurofibrillary tangles
3. *Endocrine*	Medullary carcinoma type 2 diabetes mellitus	Procalcitonin Proinsulin	Thyroid Islets of Langerhans
4. *Tumour-forming*	Lungs, larynx, skin, urinary bladder, tongue, eye	AL	Respective anatomic location

(AL= Amyloid light chain; AA= Amyloid-associated protein; Aβ2M= Amyloid β2-microglobulin; ATTR= Amyloid transthyretin; APrP=Amyloid of prion proteins, Aβ= β-amyloid protein).

PATHOGENESIS OF AMYLOIDOSIS



The current **World Health Organization** (WHO) classification is based on a constellation of **clinical, morphologic, immunophenotypic, and molecular genetic features**.

In the WHO classification, lymphoid malignancies are categorized based on their ontogeny to B or T cells.
In the **B lymphocyte group**, two major categories are recognized: **precursor and mature B lymphocytes.**
Among mature B cell lymphoma neoplasms, those composed of **small lymphoid cells** are common and have **overlapping features**, thus definitive diagnosis may be challenging.

Treatment and prognosis may vary from one subtype to the next, thus it is important to make the most definitive diagnosis as possible.

Common entities classified under the **mature small B cell category** which includes:
1.Nodal, extranodal, and splenic marginal zone lymphoma (NMZL, ENMZL, SMZL),

2. Mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL**), lymphoplasmacytic lymphoma** (LPL), and **low grade follicular lymphoma (FL).**

3.Other small B cell neoplasms that predominantly involve the blood and bone marrow (**prolymphocytic leukemia and hairy cell leukemia**).

Mature B-cell neoplasms

Chronic lymphocytic leukaemia / small lymphocytic lymphoma

Monoclonal B-cell lymphocytosis

B-cell prolymphocytic leukaemia

Splenic marginal zone lymphoma

Hairy cell leukaemia

Splenic B-cell lymphoma/leukaemia, unclassifiable

Splenic diffuse red pulp small B-cell lymphoma

Hairy cell leukaemia variant

Lymphoplasmacytic lymphoma

lgM Monoclonal gammopathy of undetermined significance

Heavy chain diseases: Mu, Gamma & Alpha heavy chain disease

Plasma cell neoplasms

Plasma cell myeloma variants: Smouldering (asymptomatic) plasma cell myeloma -Non-secretory myeloma -Plasma cell leukaemia

Plasmacytoma: Solitary plasmacytoma of bone - Extraosseous plasmacytoma

Monoclonal immunoglobulin deposition diseases: Primary amyloidosis- Light chain and heavy chain deposition diseases

Plasma cell neoplasms with associated paraneoplastic syndrome POEMS & TEMPI syndrome

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (**MALT lymphoma**)

Nodal marginal zone lymphoma /Paediatric nodal marginal zone lymphoma

Follicular lymphoma Testicular follicular lymphoma-In situ follicular neoplasia-Duodenal-type follicular lymphoma

Paediatric-type follicular lymphoma

Mantle cell lymphoma: Leukaemic non-nodal mantle cell lymphoma In situ mantle cell neoplasia

Monoclonal immunoglobulin deposition diseases (MIDD)

Definition

The **monoclonal immunoglobulin (Ig) deposition diseases** are closely related disorders characterized by visceral and soft tissue deposition of **aberrant Ig,** resulting in **compromised organ function.**

The underlying disorder is typically a **plasma cell neoplasm**, or rarely a **lymphoplasmacytic neoplasm**; however, the Ig molecule usually accumulates in tissue **before** the development of a large tumour burden.

Therefore, patients typically do not have overt myeloma or lymphoma at the time of the diagnosis.

There are two major categories of monoclonal Ig deposition diseases: primary amyloidosis and light chain and heavy chain deposition diseases.

These disorders appear to be chemically different manifestations of similar pathological processes, resulting in clinically similar conditions.

Primary amyloidosis

Definition

Primary amyloidosis is caused by a plasma cell or (rarely) a lymphoplasmacytic neoplasm in which the monoclonal plasma cells secrete **intact or fragments of abnormal immunoglobulin light chains** that deposit in various tissues and form a beta-pleated sheet structure **(amyloid light chain).**

The abnormal light chains include the N-terminal (variable) region and part of the constant region of the light chain. Most light chain variable (V) region subgroups are potentially **amyloidogenic.**

The amyloid tissue deposits accumulate and lead to organ dysfunction.

In most cases, **the diagnostic criteria for plasma cell myeloma (PCM) are lacking,** but there is a **moderate increase in monoclonal plasma cells in the bone marrow.**

Localization: Amyloid light chain accumulates in many tissues and organs.

The diagnostic biopsy site is typically the **abdominal subcutaneous fat pad or bone marrow.**

In most cases, the monoclonal plasma cell proliferation is in the bone marrow.

Microscopy

Bone marrow specimens vary from revealing no pathological findings to showing extensive replacement with amyloid, overt **PCM**, or (rarely) involvement with **lymphoplasmacytic lymphoma.**

The most common finding is a **mild increase in plasma cells** , which may appear normal or may exhibit any of the changes found in myeloma.

Amyloid deposits are found in the **bone marrow in about 60% of cases**. Amyloid is also present in many other tissues and organs.

On **H&E-stained sections**, amyloid is a **pink, amorphous, waxy-looking substance** with a characteristic cracking artefact.

Typically, it is found focally in **thickened blood vessel walls**, on basement membranes, and in the interstitium of tissues such as fat and bone marrow. Macrophages and foreign-body giant cells may be found around deposits.

Rarely, organ parenchyma may be **massively replaced** by amyloid. Plasma cells may be increased in the adjacent tissues.

Congo red stains amyloid pink to red by standard light microscopy, and under polarized light produces a characteristic **apple-green birefringence.**

Congo red fluorescence microscopy may be a more sensitive method for amyloid detection.

Electron microscopic studies can differentiate light-chain amyloidosis from non-amyloid immunoglobulin deposition diseases.

It is essential to characterize the amyloid type even when there is an associated serum or urine **M protein.**

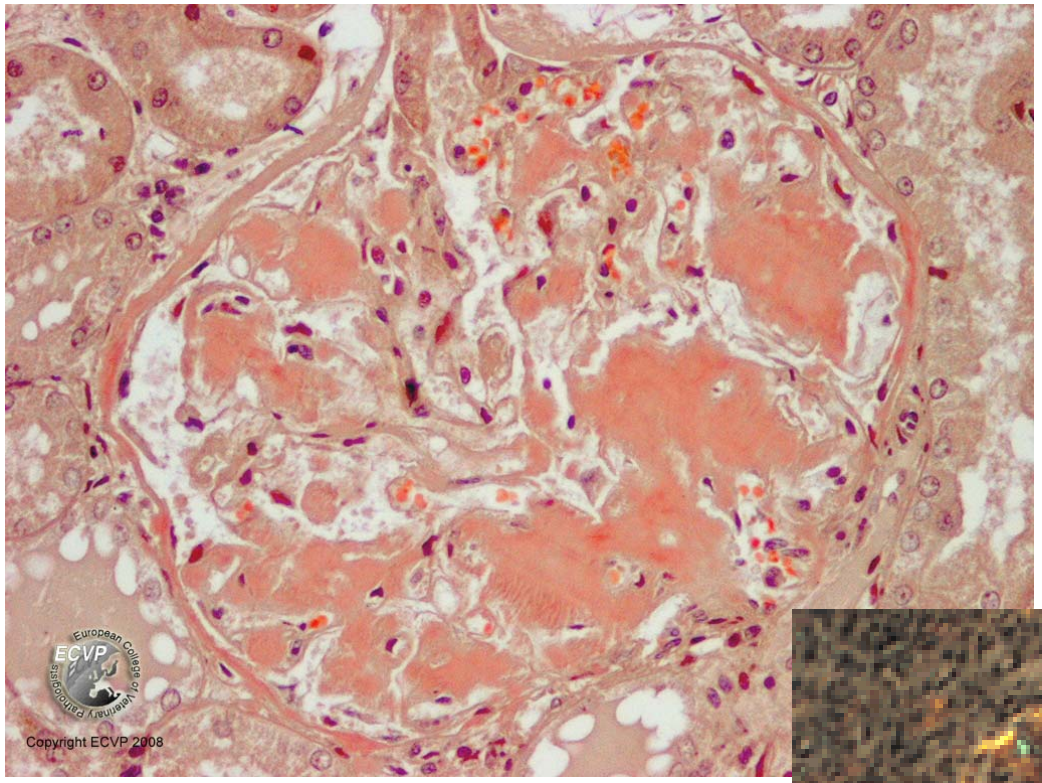
Secondary or familial amyloidosis may be incidentally present in patients with **monoclonal gammopathy of undetermined significance or another plasma cell proliferative disorder.**

Laser microdissection of the amyloid in a biopsy specimen and analysis by mass spectrometry is the most effective method of characterizing amyloid type, with nearly 100% sensitivity and specificity.

Immunophenotype
The immunophenotypic features of the monotypic plasma cells in primary amyloidosis are similar to those of PCM.

Immunohistochemical staining for immunoglobulin kappa and lambda light chains on **bone marrow sections** usually shows a **monoclonal plasma cell staining pattern,** but if the **clone is small,** it may be **masked by normal polyclonal plasma cells.**

Genetic profile
The genetic abnormalities reported in primary amyloidosis are similar to those in non-lgM monoclonal gammopathy of undetermined significance and PCM.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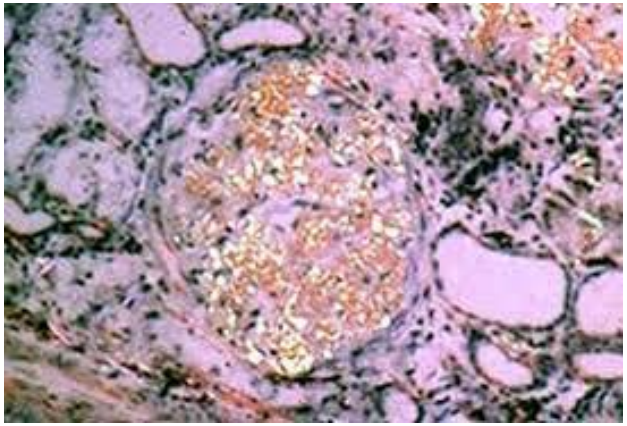
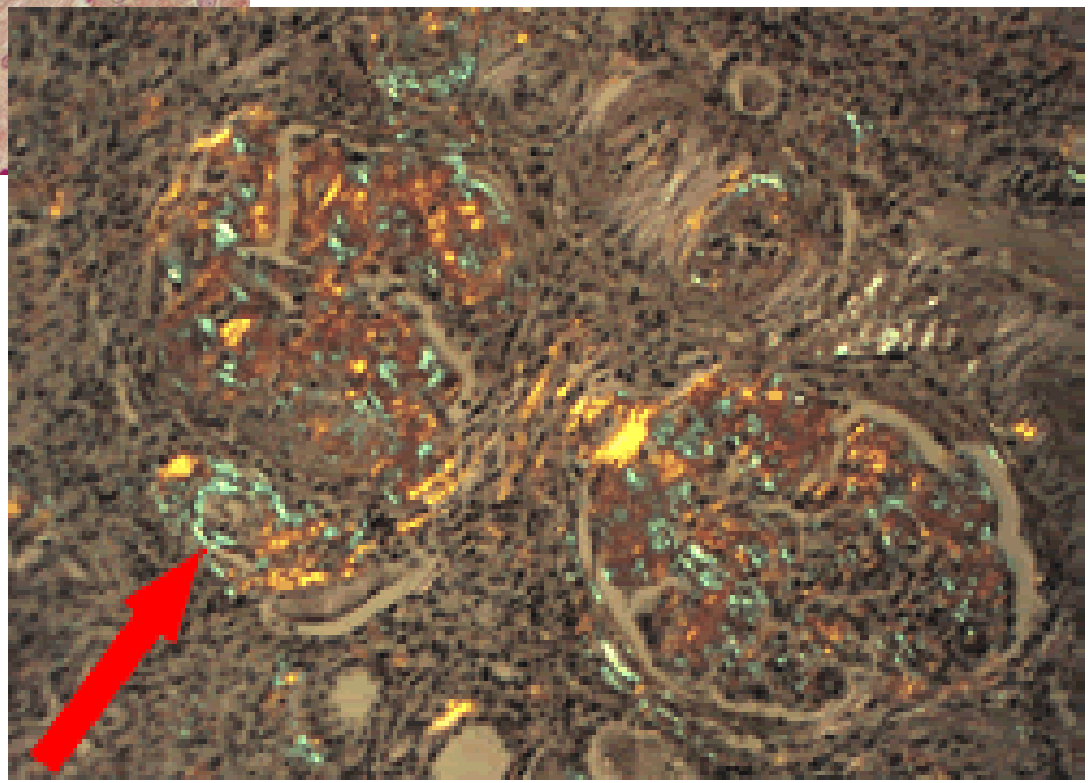




Light chain and heavy chain deposition diseases

Definition

Monoclonal light chain and heavy chain deposition diseases are **plasma cell or (rarely) lymphoplasmacytic neoplasms** that secrete an **abnormal light or (less often) heavy chain, or both,** which deposit in tissues, causing organ dysfunction, but do not form amyloid beta-pleated sheets, bind Congo red stain, or contain an amyloid P component.

These disorders comprise light chain deposition disease (LCDD), heavy chain deposition disease (HCDD), and light and heavy chain deposition disease (LHCDD)

Localization The plasma cell proliferative disorder is in the **bone marrow.** Deposition of aberrant immunoglobulin (lg) may involve **many organs**, most commonly the kidneys.

The liver, heart, peripheral nerves, blood vessels, and occasionally joints may also be involved.

Diffuse or nodular pulmonary involvement has also been reported.

There is prominent deposition of the aberrant lg on basement membranes, elastic fibres, and collagen fibres.

Microscopy

In most cases, bone marrow is involved with a plasma cell proliferative disorder, most frequently PCM. Rarely, lymphoplasmacytic lymphoma, marginal zone lymphoma, or chronic lymphocytic leukaemia is the associated neoplasm.

Deposition of the light or heavy chains is most frequently found in renal biopsies but can be observed in bone marrow and other tissues in some cases.

The aberrant Ig deposits consist of amorphous eosinophilic material that is non-amyloid and non-fibrillary, and does not stain with Congo red.

In LCDD, renal biopsies typically show nodular sclerosing glomerulonephritis. The deposits consist of retractile eosinophilic material in the glomerular and tubular basement membranes.

Immunofluorescence microscopy most often identifies kappa chains.

A hallmark of LCDD is prominent, smooth, **ribbon-like linear peritubular** deposits of monotypic Ig along the outer edge of the **tubular basement membrane**.

By electron microscopy, these deposits are typically non-fibrillary, powdery, and electron-dense.

In some cases, plasma cells are found in the vicinity of Ig deposits with an absence of the beta-pleated sheet structure by X-ray diffraction deposits in visceral organs, but most commonly, few if any are present.

Immunophenotype

LCDD has a high prevalence of kappa light chains (80%), with overrepresentation of the V kappa IV variable region. Immunohistochemistry on bone marrow sections may reveal an aberrant kappa/lambda ratio.

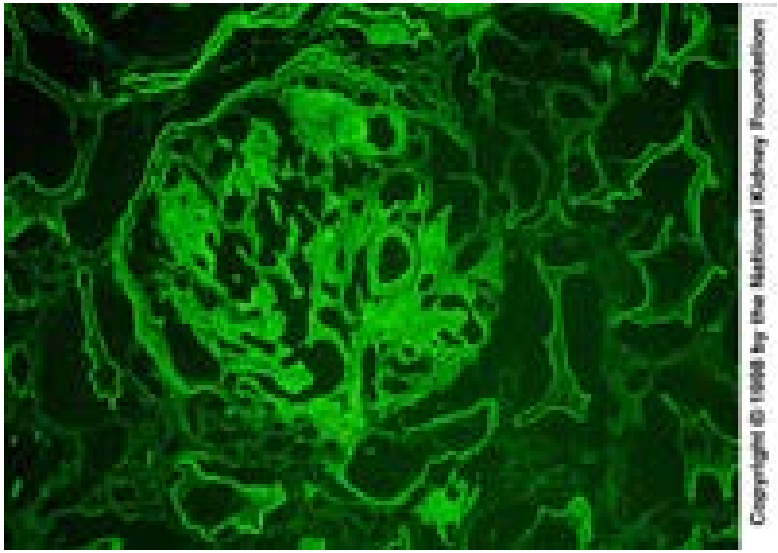
Genetic profile and pathophysiology

The genetic profile of cases associated with PCM is similar to that of other PCMs.
The M protein in non-amyloid Ig deposition diseases has undergone structural change due to deletion and mutation events.

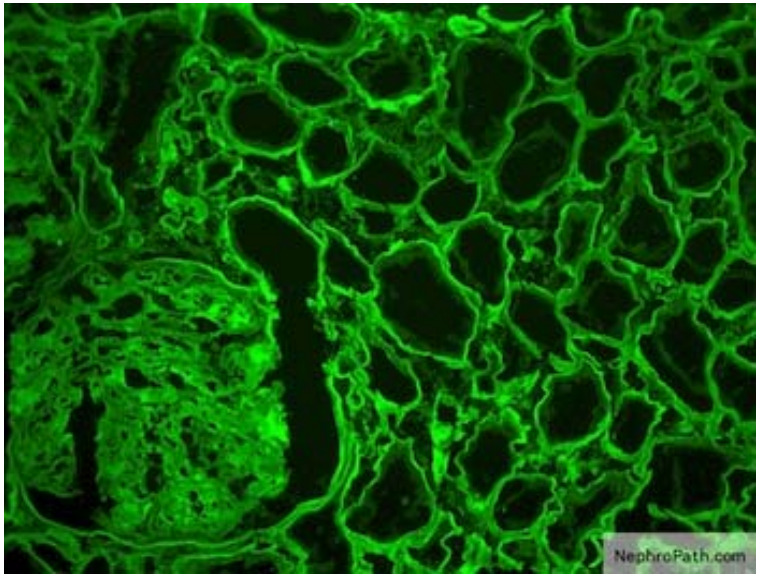
In LCDD, the primary defect involves multiple mutations of the IG light chain variable region, with kappa light chain of V kappa IV type notably overrepresented.

In HCDD, the critical event is deletion of the CH1 constant domain, which causes failure to associate with heavy chain binding protein, resulting in premature secretion.

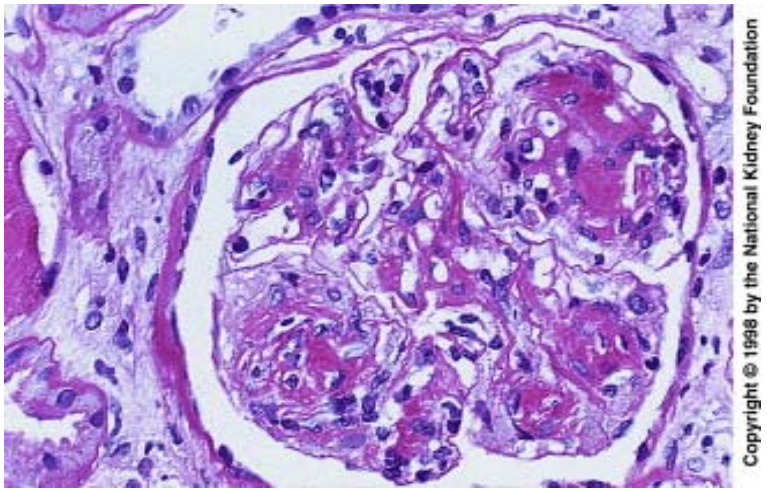
In HCDD, the variable regions also contain amino acid substitutions that cause an increased propensity for tissue deposition and for binding blood elements.



Glomerular capillary loop, mesangial staining, and linear tubular staining are characteristic of light chain deposition disease. Either kappa or lambda light chain paraprotein may cause light chain deposition disease, although kappa more commonly is the culprit (antibody to kappa light chain, immunofluorescence; original magnification x200).



Positive GBM and
TBM staining
for kappa light chain on IF

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