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HHV-8-negative Multicentric Castleman disease presenting as a crescentic immune complexes membranoproliferative glomerulonephritis

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SUMMARY

Multicentric Castleman disease (MCD) is a rare polyclonal lymphoproliferative disorder. It is associated with various renal manifestations. We report here a case of HHV8 negative multicentric Castelman disease with membranous proliferative glomerulonephritis and extracapillary proliferation with good response to corticosteroids, anti-CD20 and cyclophosphamide therapy.

Key Words: Multicentric Castleman disease - membranous glomerulonephritis - extracapillary proliferation.

BACKGROUND

Castleman disease (CD) is a rare [1] [2] polyclonal lymphoproliferative disorder characterised by 3 histological patterns: hyaline-vascular, plasma cell and plasmablastic. [2]. Clinical presentation is heterogeneous [2], and classified into unicentric or multicentric disease [1] [2]. Unicentric Castleman disease (UCD) is the most frequent type [3]. It involves a single lymph nodal region, and symptoms are mainly due to local lymph node enlargement [3] .Its surgical resection is curative [3] .In contrast, multicentric Castleman disease (MCD) involves multiples lymph nodes area [4] [5] [6]. It is subclassified into human herpes virus 8 (HHV8) related or not [5] [6] [7]. MCD is a severe multi-systemic disease, with non-specific symptoms such as lymphadenopathy, fever, weight loss, fatigue, oedema and ascites [3] [8]. The high level of cytokines production, notably interleukin-6 (IL6) [7] can affect each system, and eventually lead to multi organ failure [6]. Corticosteroids, monoclonal antibodies targeting B cells and IL-6 pathway are cornerstones of the treatment [3] [5] [9] [10]. Nevertheless, recurrence is frequent and prognosis poor [10]. Renal involvement is also common [11] and various histological patterns have been described. As membranous proliferative glomerulonephritis has been previously reported, extracapillary proliferation has not been described yet.

We herein report a case of case of HHV8 negative multicentric Castelman disease with membranous proliferative glomerulonephritis and extracapillary proliferation.

Case presentation

A 48 years old man from the Middle East presented to our hospital because of night sweats, lower extremities edema and a weight loss of 12 kg in 3 months.

He had a previous medical history of dyslipidemia, severe obesity (body mass index of 35 kg/m2), and 25 pack year previous smoking. 2.5 months before admission, he was admitted

to another hospital because of an acute left limb pain. A multi-segmental artery occlusion of the limb was then diagnosed which justified an anticoagulation by vitamin K antagonist.

The patient had no other complaints. Except for increased blood pressure and bilateral pitting edema, clinical examination was normal.

INVESTIGATIONS

Blood test showed acute renal failure (creatinemia 200 umol/L(N: 62-106 umol/L), estimated glomerular filtration rate 13 ml/min/1.73m2, urea 5 mmol/L) with hypoalbuminemia (26 g/l), and a high inflammation state (sedimentation rate over 100 mm/h, CRP 90 mg/l). Urinalysis showed erythrocytes cast and mild leukocyturia. Twenty-four-hour urine protein excretion was 9.24 g/day. Immunofixation showed a polyclonal hypergammaglobulinemia without monoclonal spike. Rheumatoid factor and anti-neutrophil cytoplasmic antibody were negative, with normal C3 and C4 levles. Search for cryoglobulinemia was negative. Anticardiolipin (aCL) and anti-b2 glycoprotein-I (anti-b2GPI) were negative. PCR Viral testing for CMV, EBV, hepatitis B and C, HIV and human herpes virus 8 (HHV8) were also negative. Bacterial serologies for leptospirosis, *Brucella spp*, *Borellia burgdorferi*, *Coxiella burnetti*, *Bartonella henselae*, and *Treponema pallidum* hemagglutination assay, as well as toxoplasma serology were negative. Interferon Gamma Release Assay was negative as well as urine culture for mycobacteria. Beta-d-glucan was also negative.

Chest radiography revealed bilateral pleural effusion. Kidney ultrasound with Doppler showed no anomaly. Considering nephrotic syndrome, a renal biopsy was performed. It demonstrated a membranoproliferative pattern with an extracapillary proliferation (Figure 1 and 2). Immunofluorescence was positive for IgA, IgG, IgM, C3 and C1q deposits (full house) (Figure 3 and 4). 2-FDG positron emission tomography (PET) scan revealed supra and sub-diaphragmatic hypercaptive adenopathies, a mediastinal mass with hypercaption and splenic increased FDG uptake. A left axillary lymph node resection was performed. Pathology determined Castleman-like pattern with hyperplasic adenopathy, associated with follicular

hyperplasia, interfollicular expansion, significant polytypic plasma cells and circularly capillary penetrated some germinal centers. There was no evidence of lymphoma. HHV8 and EBV immunohistochemestery were negative. Moreover, fewer than 10% of plasma cells were IgG4 positive. Interleukine-6 (IL-6) was measured at 18.5 µg/l which was very high for the norms of our laboratory (N<1 µg/l);

DIFFERENTIAL DIAGNOSIS

We concluded that this patient suffered from HHV8 negative multicentric Castleman's disease with crescentic immune complex glomerulonephritis with a membranoproliferative pattern (ICGNMP). Treatment was initiated with corticosteroids, anti-CD 20 therapy with rituximab, and cyclophosphamide.

OUTCOME and FOLLOW-UP

The patient quickly improved: few days after corticoids administration the fever and inflammatory markers decreased. As proteinuria resolved after 2 months, renal function improved slowly and one year later creatinemia was 144 umol/l, estimated glomerular filtration rate of 45 ml/min/1.73m2. FDG positron emission tomography scan was repeated 3 months later. Lymphadenopathies regressed and the mediastinal mass partially resolved without hypercaption.

Discussion

Up to 54% of MCD, mostly in plasma cell or mixed cellular type, are associated with nephropathy, defined as hematuria, proteinuria or renal insufficiency [11] [12][13] [14]. The two main histological patterns are thrombotic microangiopathy (TMA) (60%) and amyloidosis (20%) [15] [16]. Those histological patterns may be explained by the dysregulation of IL-6 production and vascular endothelial growth factors (VEGF) in the lymph node mantle [15] [17] [18] [19]. Indeed, IL-6 pro inflammatory cytokine stimulates precursor of the AA protein, and VEGF that leads to TMA, notably due to angiogenesis [20] [21]. Nevertheless, our patient had proliferative glomerulonephritis. We hypothesized that the high level of IL-6 promoted B cells

activation inducing immune complexes, “trapped” in the subendothelial space of the glomeruli and determining proliferative glomerulonephritis. The nature of the immune deposit is in our opinion the clue to the etiology (i.e C3 dominant deposit should lead to exploration for a C3 glomerulopathy, monoclonal deposit to a monoclonal gammapathy of renal significance, etc.) [22]. ICMPGN is mainly due to lupus or post infectious nephritis. It has been also rarely described in asian origin patients with idiopathic Castleman’s disease [23]. Our case illustrates that Castleman’s disease should now be part of the differential diagnosis in caucasian patients as well. Our patient had C1q and C5b9 deposition, suggesting complement activation. In case of complement activation, eculizumab, an anti-C5 monoclonal antibody could be used as a rescue therapy in resistant or severe MPGN due to Castleman disease [22].

Conflicts of interest

The authors declare that they have no conflicts of interest related to this study.

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Figure 1: Renal biopsy showed an extracapillary proliferation with cellular crescents (FAOG, 400x)

Figure 2: Renal biopsy showed a membranoproliferative glomerulonephritis pattern: flocculi are lobulated with a duplication of the membrane. Endocapillary and extracapillay proliferations were also observed

Figure 3: Immunofluorescence: IgG deposits were observed within mesangium and membranes of glomeruli (400x).

Figure 4: Immunofluorescence: C3 deposits were observed within mesangium and membranes of glomeruli (200x

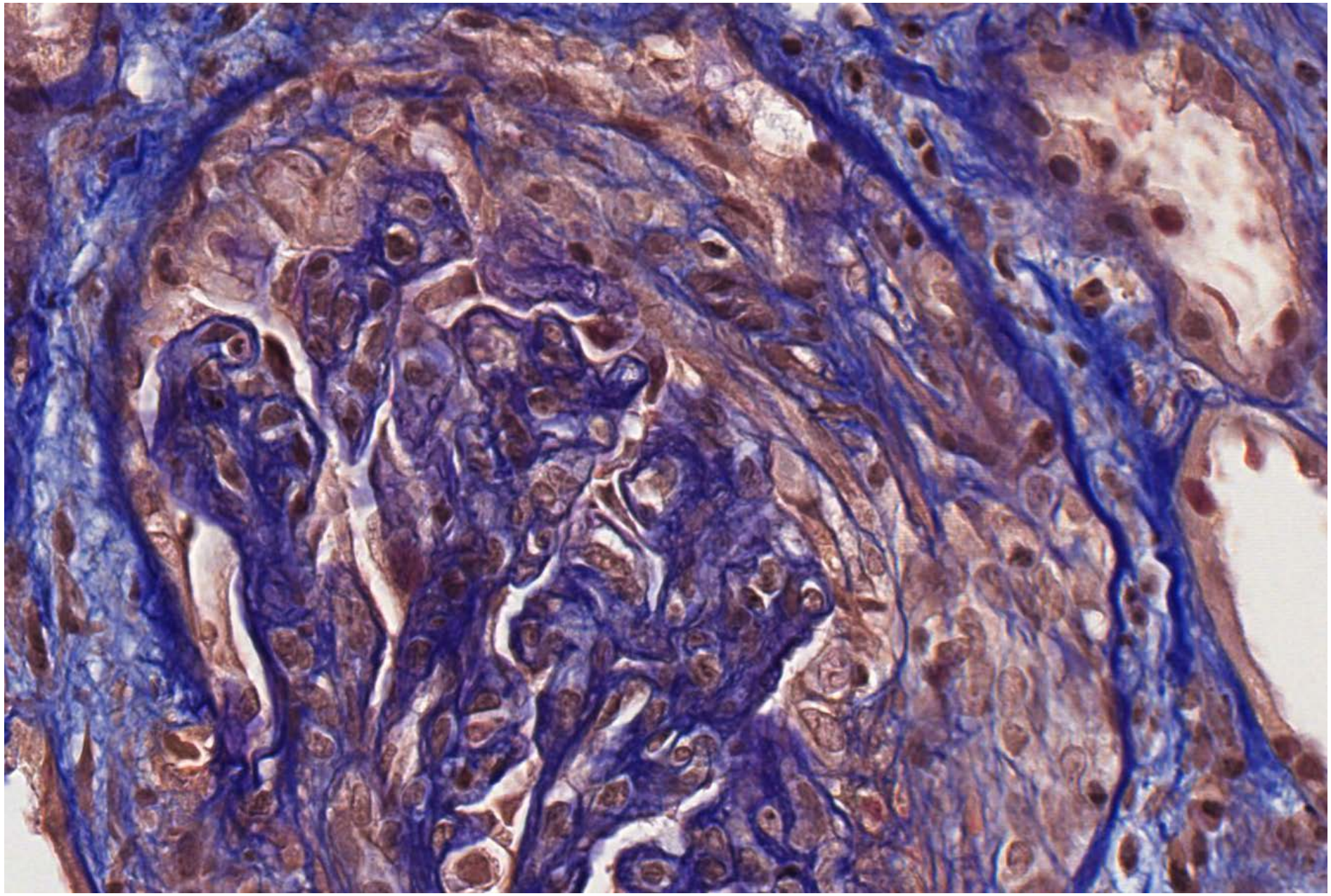
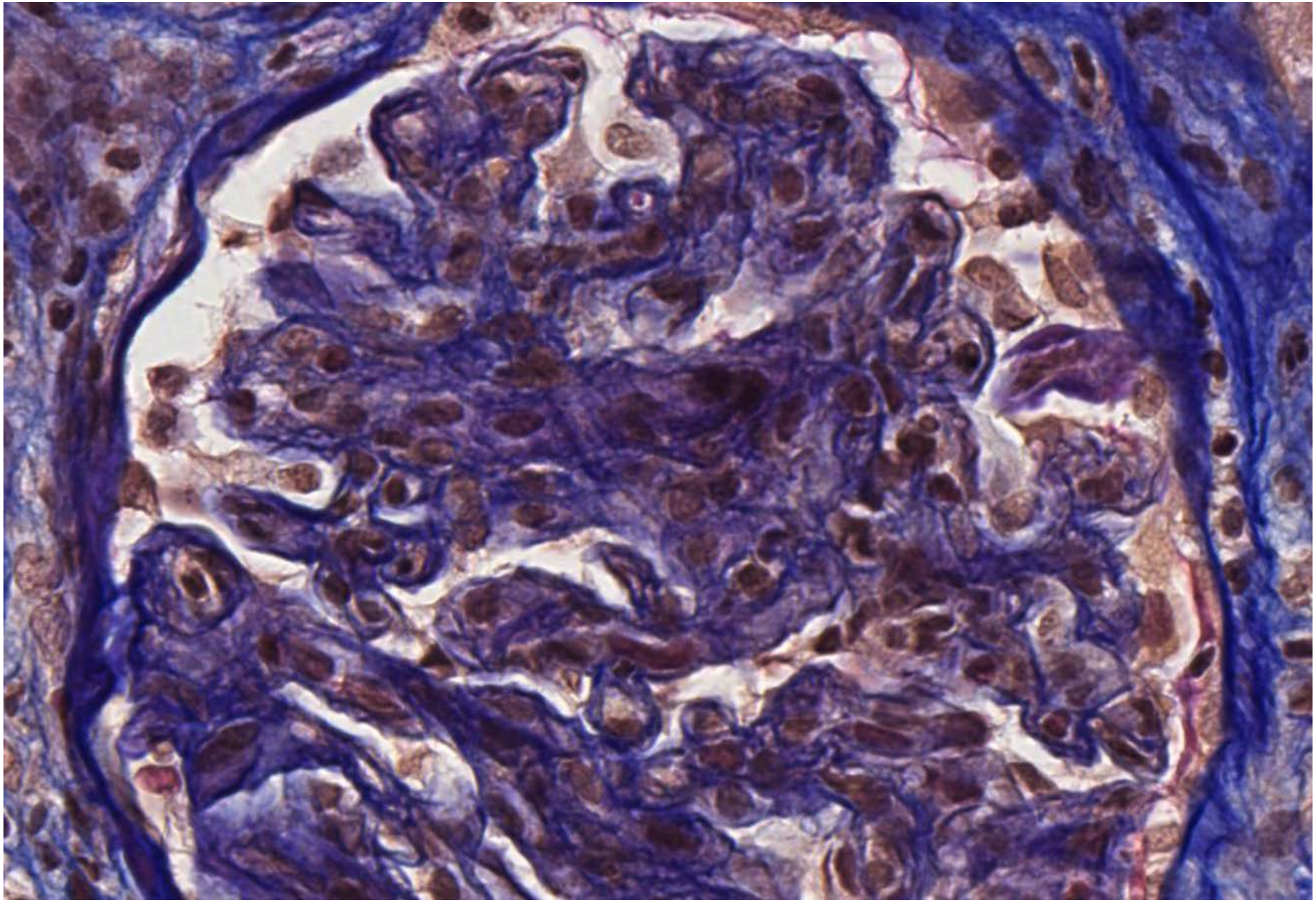


Fig 1

Fig 2



IgG

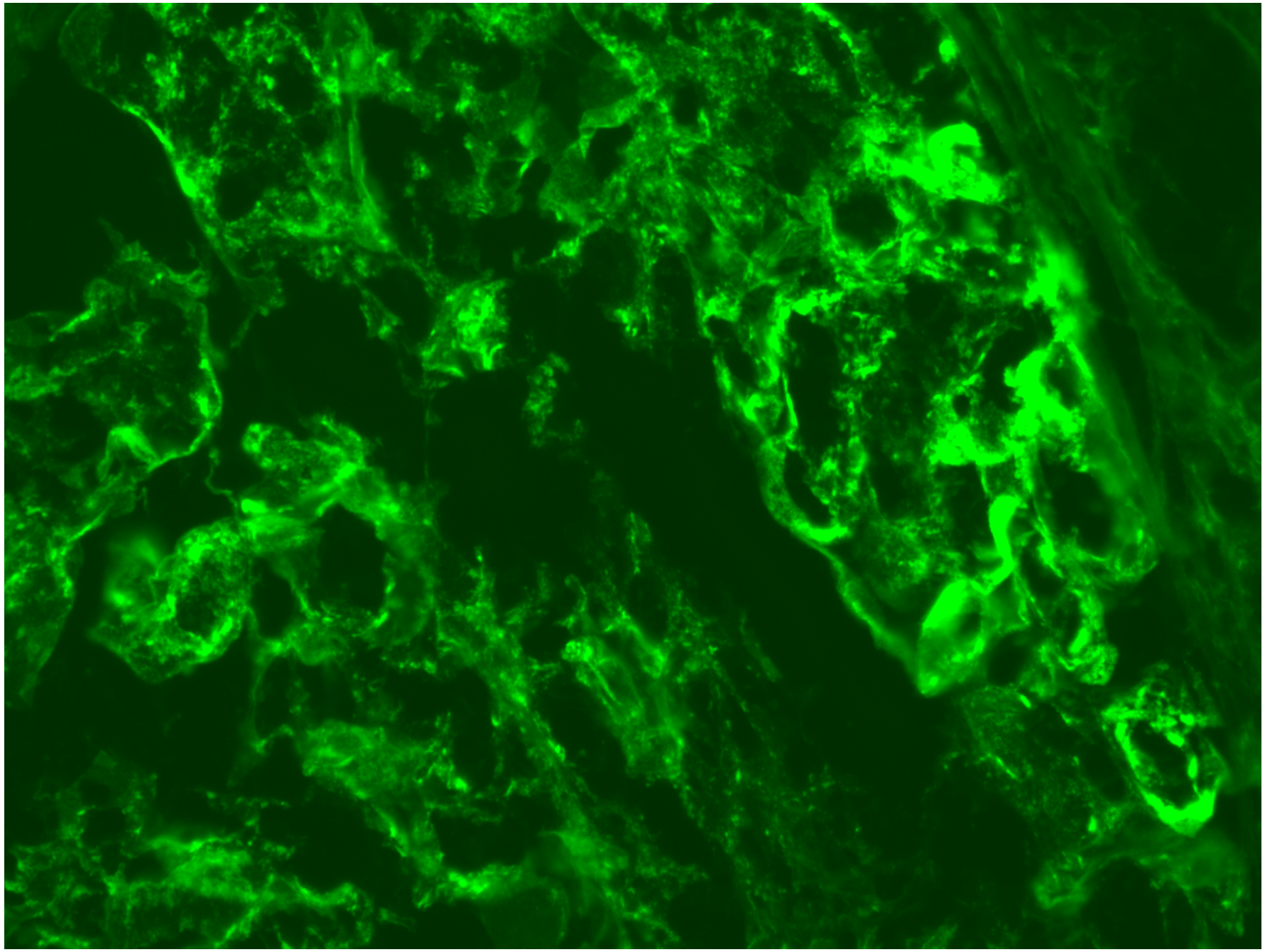


Fig 3

C3

Fig 4