

# Refractory secondary thrombotic microangiopathy in two systemic disorders with remission after autologous haematopoietic stem cell transplantation: a case series

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## Case Report

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# Abstract

## Background

Secondary thrombotic microangiopathy (TMA) may complicate catastrophic antiphospholipid syndrome (CAPS) and monoclonal gammopathy-associated disorders. In refractory disease, conventional haematological markers may not reflect ongoing organ injury, and evidence supporting autologous haematopoietic stem cell transplantation (AH SCT) is limited.

## Case presentation

Patient A was a 15-year-old girl with systemic lupus erythematosus and antiphospholipid syndrome who subsequently developed CAPS with multiorgan involvement and dialysis-dependent kidney failure. Intensive immunosuppression, plasma exchange, anticoagulation, and complement inhibition achieved partial clinical and haematological control, but serious cardiac and cerebrovascular events occurred thereafter, accompanied only by transient changes in platelet count and lactate dehydrogenase. Following AH SCT in 2018, relevant autoantibodies became negative, and no clinical recurrence of systemic lupus erythematosus, antiphospholipid syndrome, or TMA occurred during more than 8 years of follow-up; she subsequently underwent successful kidney transplantation. Patient B was a 37-year-old man with an IgG-lambda monoclonal protein, plasmacytomas, features of Castleman disease, and a POEMS syndrome-like phenotype without polyneuropathy. Serial kidney biopsies demonstrated progressive kidney-limited TMA despite normal systemic haemolysis markers and treatment with ravulizumab and clone-directed therapy. Kidney, constitutional, ophthalmological, and cardiac manifestations progressed. Eight months after AH SCT in 2025, symptoms and inflammatory markers improved, estimated glomerular filtration rate increased from 35 to 70 mL/min/1.73 m<sup>2</sup>, urinary protein-to-creatinine ratio decreased from 2.05 to 1.17 g/g, and the monoclonal protein decreased from 4.6 to 2.0 g/L.

## Conclusions

These cases illustrate that organ injury in secondary TMA may progress despite partial systemic response and without persistent abnormalities in conventional haematological markers. Assessment should therefore integrate organ-specific trajectories with systemic disease activity, with targeted reassessment when clinical findings and laboratory markers are discordant. Clinical improvement followed AH SCT in both patients, including durable remission in Patient A. Together with previous reports, these observations support considering AH SCT as a therapeutic option in selected patients with severe secondary TMA associated with a potentially transplant-responsive autoimmune or clonal disorder. Although published experience has predominantly involved treatment-refractory disease, this does not establish that AH SCT should be confined to rescue therapy; its optimal timing remains unknown. These observations do not establish the magnitude of any treatment effect or a routine organ-surveillance protocol.

# Background

Systemic lupus erythematosus (SLE), a chronic autoimmune disease, may be complicated by secondary antiphospholipid syndrome (APS) that is associated with thromboses and obstetric complications. Catastrophic APS (CAPS) is the most severe form of APS, characterized by rapidly developing multiorgan involvement caused by thromboses and thrombotic microangiopathy (TMA), with a mortality rate of approximately 40–50% [1].

POEMS syndrome is a rare multisystem disorder caused by an underlying monoclonal plasma cell proliferation and a variable number of manifestations listed in the acronym – Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, Skin changes [2]. Additional manifestations may include sclerotic bone lesions, plasmacytic Castleman disease, papilledema, peripheral oedema, ascites, thrombocytosis and/or polycythaemia, venous and/or arterial thrombosis, and kidney, pulmonary, or cardiac impairments [3]. TMA, a syndrome that is often associated with aberrant complement activation, can also be caused by monoclonal gammopathy (MG) and it has been shown, that purified IgG fractions of patients with MG-associated TMA can induce complement activation, while purified monoclonal immunoglobulins (MI) can in some cases act as an anti-factor H antibody [4–6].

In both advanced SLE and many MG-associated disorders, autologous haematopoietic stem cell transplantation (AHSCT) represents a last-resort treatment option for refractory disease, but the role of AHSCT in patients with TMA in these settings is poorly defined. In this paper, we present two rare and clinically challenging cases of life-threatening secondary TMA that did not respond to standard treatment and ultimately abated after AHSCT: a female patient with SLE and CAPS, and a male patient with POEMS syndrome-like clonal plasma cell disorder with features of Castleman disease. By describing these two cases, we aim to demonstrate the diagnostic and therapeutic challenges and the possible role of AHSCT in the management of refractory secondary TMA.

## Patient with SLE, CAPS and refractory secondary TMA

Patient A first presented in 2003 at age 15 with SLE manifesting as chorea, malar rash, oral aphthae, photosensitivity, pancytopenia, presence of lupus anticoagulants (LA) and all of the following antibodies: antinuclear antibody (ANA), antibodies against double stranded DNA (anti-dsDNA) and against beta-2-glycoprotein ( $\beta$ -2-GPI). Brain magnetic resonance imaging (MRI) showed multiple small ischaemic lesions. She was treated with high-dose methylprednisolone (MP) and monthly intravenous (IV) cyclophosphamide (CYC), achieving stabilisation, followed by maintenance MP, azathioprine (AZA), and acetylsalicylic acid.

After stopping treatment for about two years, she had an exacerbation in January 2008 with thrombocytopenia, Coombs-positive haemolytic anaemia, and worsening of kidney function with proteinuria. A kidney biopsy showed lupus nephritis WHO class II with predominating TMA features. MP and AZA were reinstated and warfarin was added. In September 2008 she was hospitalised for severe headaches and vomiting, with several small acute ischaemic lesions on brain MRI. MP dose was

increased and anticoagulation monitored more closely. In 2010 she was hospitalised twice more, for necrotic finger lesions treated with iloprost and for transient left-sided hemiparesis; AZA was switched to chloroquine, later discontinued for maculopathy.

In March 2017 she was admitted with a history of recent high fever (39°C), productive cough, oral ulcers and 6-kg weight loss. Chest CT confirmed diffuse multiple infiltrates bilaterally and infectious causes were excluded. Laboratory findings confirmed TMA (low platelets and haptoglobin, elevated LDH and schistocytes), anticardiolipin antibodies (aCL) and anti-phosphatidylserine/prothrombin antibodies (aPS/PT) (Supplementary Table 1), with normal ADAMTS13 activity (78.1%), negative Shiga toxin, and no signs of disseminated intravascular coagulation. High-dose MP was started on day 3, followed by rituximab (RTX) and regular plasma exchange from day 4. On day 7 she developed status epilepticus and was transferred to the intensive care unit (ICU). CYC and IV immunoglobulins (IVIG) were added. Over the following weeks she developed fulminant CAPS with multiorgan failure affecting the central nervous system (ischaemic changes), lungs (acute respiratory distress syndrome – ARDS), heart (transiently impaired systolic function and extensive pericardial effusion), gastrointestinal tract (signs of extensive mucosal thrombosis), liver (multiple infarcts), and spleen (multiple infarcts), as well as acute kidney failure requiring haemodialysis (HD) due to prolonged anuria. Heparin was briefly withheld because of severe thrombocytopenia and a haemorrhagic transformation of the ischaemic brain lesions with transient right-sided hemiparesis. The implemented therapy resulted in a temporary improvement and transfer back to the ward, but she had to be readmitted to the ICU on two additional occasions, once because of epileptic seizures and the second time because of ARDS. Subsequent hospitalization was complicated by two episodes of sepsis (*Escherichia coli* and *Staphylococcus epidermidis*) which prevented intensifying immunosuppression. TMA persisted throughout, and she lost 17 kg (nadir 38 kg; body mass index (BMI) 14.3). On day 103 eculizumab (ECU) was started, with cyclosporine (CsA) added shortly after (Supplementary Table 2); this combination achieved remission, with recovery of CNS, lung, cardiac, gastrointestinal, and liver involvement and normalised platelet counts (Fig. 1). Complement testing before this treatment showed classical-pathway activation (44%, reference range 55–145%), low C3 (0.55 g/L, reference range 0.90–1.80 g/L), normal C4 and serum C5b9 and negative antibodies against C1q, Factor H, and C3-nephritic factor. She was discharged in August 2017, markedly improved but still dialysis dependent.

In February 2018, she experienced cardiac arrest due to ventricular fibrillation during dialysis, resuscitated after 10 minutes, with a transient fall in platelets and rise in LDH. Coronary angiography excluded coronary artery disease and cardiac ultrasound showed a normal systolic function with only mild diastolic dysfunction. Implantation of an implantable cardioverter-defibrillator (ICD) was planned, but while waiting she had a second arrest (pulseless electrical activity), again with transient platelet/LDH changes, resuscitated after 4 minutes. The next day she had a seizure with transient right-sided hemiparesis. Brain CT imaging showed extensive chronic changes and two small acute lesions. The ICD was implanted in March 2018.

A multidisciplinary nephrology–haematology–rheumatology consultation concluded that the disease remained only partially controlled despite ECU, CsA, MP, and anticoagulation, and recommended AHSCT. After discussion of risks and benefits, the patient consented. The patient underwent lymphodepleting conditioning with cyclophosphamide 50 mg/kg daily, given with mesna prophylaxis for 4 days (day – 5 to day – 2), together with rabbit anti-T-lymphocyte globulin (ATLG; Grafalon®) administered in escalating fractionated doses over the same 4-day period (day – 5 to day – 2), to a cumulative dose of 20 mg/kg, and underwent AHSCT on April 23, 2018 ( $2.3 \times 10^6$  CD34<sup>+</sup> cells/kg, BMI 17.3). The procedure was complicated by spontaneous iliopsoas bleeding with a significant haemoglobin drop; the bleeding vessel was not amenable to intervention, so heparin was held and resumed once the haematoma decreased on CT. Haematopoietic recovery began on day 8, with platelet engraftment by day 16. ECU, CsA, and MP were stopped after AHSCT, and hydroxychloroquine 200 mg three times weekly (post-HD) was started.

During follow-up she had no further TMA or SLE exacerbations, anti-dsDNA and  $\beta$ -2-GPI were negative, and C4 had already normalised before AHSCT, but aCL and aPS/PT became negative and C3 normalised only afterward (Fig. 2). Activated partial thromboplastin time, previously prolonged off heparin (as typical in APS), also normalised after AHSCT, suggesting disappearance of LA. Discontinuing anticoagulation was discussed but, after shared decision-making, treatment was continued.

On April 30, 2020, she received a deceased-donor kidney transplant, with tacrolimus and mycophenolate mofetil as long-term maintenance along with hydroxychloroquine until renewed development of maculopathy in 2021. At last follow-up in June 2026, more than 8 years after AHSCT, she remained free of any clinical or laboratory signs of SLE and APS, with an eGFR of 81 mL/min/1.73 m<sup>2</sup> and UPCR 0.20 g/g.

### **Patient with refractory secondary TMA associated with POEMS syndrome-like clonal plasma cell disorder with features of Castleman disease**

Patient B, a 37-year-old man, was first hospitalised in May 2023 with a 3-day history of chest pain radiating to the left arm, and new exertional dyspnoea, without fever or signs of infection. Troponin I was elevated up to 289 ng/L (normal < 34 ng/L). Coronary angiography was normal and cardiac MRI showed signs of focal oedema on T2 sequences, with subepicardial and mid-wall late gadolinium enhancement (LGE), and a normal ejection fraction, interpreted as myocarditis. Symptoms resolved spontaneously and troponin normalised; he later recalled an almost identical symptomatic episode in March 2023, with slightly elevated troponin levels as well.

In August 2023 he was referred for arterial hypertension, headaches and heavy proteinuria (UPCR 3.45 g/g) with normal kidney function, alongside malaise and night sweats since May. Work-up identified an IgG-lambda monoclonal immunoglobulin (MI, 3.2 g/L). A kidney biopsy was performed in November 2023, showing active glomerular TMA, with glomerular mesangiolysis and segmental double glomerular basement membrane contours consistent with TMA, no vascular TMA, no immune deposits, and minimal chronicity (GSCL 0%, IFTA < 5%). Throughout the disease course he never had laboratory evidence of TMA – LDH and haptoglobin were normal, schistocytes absent, and platelets persistently elevated (389–632  $\times 10^9$ /L). Bone marrow biopsy showed trilineage hypercellularity and reticulin expansion, without myeloma.

Serological testing (ANA, anti-dsDNA, aCL,  $\beta$ -2-GPI, aPS/PT), LA and a comprehensive complement work-up (C3, C4, C5b9, pathway activity, anti-C1q, anti-factor H, C3-nephritic factor) were all negative or normal, as was genetic testing for atypical HUS. He started treatment with ravulizumab.

There was no substantial improvement by March 2024 – blood pressure remained high, malaise and night sweats recurred, and proteinuria stayed elevated with preserved kidney function. A second kidney biopsy revealed progression of TMA (global mesangiolysis, erythrocyte extravasation, vascular TMA) with chronic changes (30% GSCL, segmental glomerulosclerosis, 20% IFTA). A chest radiograph incidentally showed an osteolytic lesion in the right clavicle, metabolically active on a  $^{18}\text{F}$ -FDG PET/CT scan, along with a soft tissue mass behind the right clavicle and another osteolytic lesion in the left iliac bone (Figs. 3 and 4). Anti-factor H antibodies were detected for the only time. A decision was made to start treatment with high doses of oral MP and RTX, which resulted in resolution of malaise and night sweats.

In April 2024 a biopsy of the osteolytic lesion in the right clavicle confirmed plasmacytoma. In consultation with the haematologist RTX was stopped and in May 2024 he started treatment with daratumumab, bortezomib, lenalidomide (DVR), whereby dexamethasone was omitted due to concomitant treatment with high doses of MP (information on all the immunosuppressive and immunomodulatory treatment is in Supplementary Table 3). He received three cycles of therapy, underwent filgrastim-only stem-cell mobilization and collection, and then proceeded to two additional cycles with bortezomib cut short because of nausea. Treatment was subsequently reduced to lenalidomide maintenance because of logistical constraints and was completely stopped in February 2025 because of diarrhoea and lack of substantial clinical benefit. Over this period eGFR fell from 107 to 58 mL/min/1.73 m<sup>2</sup>, and UPCR rose from 2.03 to 2.75 g/g, while the MI remained stable (2.7 g/L). The retroclavicular mass was unchanged, and a June 2025 biopsy showed Castleman disease-like histology (mixed hyaline-vascular/plasma-cell type); HHV-8, CMV, EBV, and HIV were negative and IL-6 was normal (VEGF unavailable).

In August 2025 the disease progressed with recurrence of hypertension, visual disturbance, exertional dyspnoea, sweating, malaise and a 5-kg weight loss. Bilateral papilledema and MRI signs of intracranial hypertension were found, and eGFR fell to 44 mL/min/1.73 m<sup>2</sup>. A third kidney biopsy showed advancing chronic active TMA lesions, affecting all glomeruli with double contours of glomerular basement membrane, chronic mesangiolysis, endothelial swelling and subendothelial widening, with vascular narrowing of > 50% (vascular TMA), and diffuse acute tubular injury (Fig. 5). Abdominal ultrasound showed hepatomegaly. Cardiac MRI showed cardiomyopathy with diffuse T1 enhancement and normal T2 and LGE, which was interpreted as diffuse myocardial fibrosis, with normal ejection fraction, and a small pericardial effusion.  $^{18}\text{F}$ -FDG PET/CT showed expansion of the retroclavicular mass and left iliac bone lesion. The latter was biopsied and plasmacytoma was confirmed for the second time. There were no clinical signs of neuropathy, and electromyography was normal.

Following consultation with international experts, siltuximab and a bortezomib/dexamethasone/thalidomide/doxorubicin/CYC/etoposide/RTX regimen were considered, but

doxorubicin was avoided given the cardiac disease. In consultation with haematologists, AHSCT was instead recommended and performed on September 22, 2025 (conditioning with melphalan 140 mg/m<sup>2</sup> body surface area, receiving 4.0 x 10<sup>6</sup> CD34<sup>+</sup> cells/kg). Prior to the transplantation the kidney function worsened to an eGFR of 35 mL/min/1.73 m<sup>2</sup>, UPCR 2.05 g/g, MI 4.6 g/L. The procedure was complicated by *Clostridium difficile* colitis that responded to fidaxomicin with no other complications. The first signs of haematopoietic recovery were observed on day 12, and platelet engraftment had occurred by day 18.

At last follow-up in May 2026, he was clinically improved with no major complaints: blood pressure 140/77 mmHg, eGFR of 70 mL/min/1.73 m<sup>2</sup>, UPCR 1.17 g/g, MI 2.0 g/L (timeline of major clinical events and key laboratory data in Supplementary Table 4).

## Discussion

AHSCT is a well-recognized treatment for certain haematological malignancies. In multiple myeloma it is the standard of care for eligible patients, successfully lowering the plasma cell clone [7]. It is an established treatment option in POEMS syndrome, with a good haematological response and lower rates of relapse, progression and mortality compared to patients with multiple myeloma [8, 9].

For the past three decades, AHSCT has also been used for refractory autoimmune diseases (AD), particularly multiple sclerosis and systemic sclerosis, where it is now the standard of care for challenging patient groups [10]. The concept has been described as a “resetting” of the immune system with ablation causing an elimination of the autoreactive immune cells and repopulation leading to a more self-tolerant immune system [11]. In SLE the treatment is now considered a clinical option for refractory cases, after careful assessment of risks and benefits [10]. Published series and a systematic review on AHSCT in patients with APS secondary to SLE have confirmed favourable outcomes including disappearance of LA activity and APS-related antibodies with most patients successfully discontinuing anticoagulant therapy [12, 13]. This treatment, however, is not without significant risks. A recent retrospective study on complications after AHSCT for AD has identified a 10-year cumulative incidence of secondary ADs of 10.3%, new post-transplant cancers 4.1%, endocrine complications 16.2%, and cardiovascular complications 14.7%, with a 10-year mortality rate of 16.5% [14].

The role of AHSCT in the treatment of diseases in which the primary process is TMA is not well defined. In the systematic review of AHSCT in patients with SLE-related APS only 2 of 46 patients had CAPS; both had favourable outcomes [13]. There are also some sporadic case reports of successful treatment, including a patient with resistant undefined thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, and three patients with CAPS, one leading to myocardial necrosis, the second associated with purpura, kidney impairment, and pneumonitis, and the third in conjunction with MALT lymphoma [15–18]. On the other hand, AHSCT itself can cause TMA and a post-transplantation occurrence of de-novo APS [19, 20].

Patient A had a difficult course of SLE with predominant TMA-related complications throughout the disease course. During the 6-month hospitalisation in 2017 we were unable to induce remission despite

treatment consisting of high dose MP, CYC, RTX, IVIG and plasma exchanges. Specifically, we were unable to stop TMA, the platelet counts remained low and LDH elevated for months, which complicated further treatment with CYC. Intensification of therapy was also hindered by two episodes of sepsis. We were reluctant to add hydroxychloroquine because of prior chloroquine-associated maculopathy and concern that QTc prolongation or arrhythmia would pose additional risk during active TMA. No additional supplemental RTX was given after plasma exchange, potentially resulting in reduced drug exposure and contributing to the unfavourable clinical course. Given the contemporary reports of success of anti-complement therapy in some cases of SLE-related APS, we decided to try treatment with ECU with no improvement after first two doses. Consequently, CsA was added despite concerns about its potential to exacerbate the TMA. Thereafter, the TMA subsided, although the contribution of ECU, CsA, or their combination could not be determined.

Further evidence of the importance of persistently high aCL and aPS/PT in this case is suggested by the changes prior to and after AHSCT. It seems that the combination of ECU, CsA, and MP did stabilize but not fully control the disease, as the antibodies remained high, particularly aPS/PT, and C3 did not completely normalise. Progression of cardiac and cerebrovascular disease led us to the conclusion that additional therapy was needed. Newer therapies such as belimumab, anifrolumab and voclosporin could have been an option in this situation, but they were not available at the time, and their effect on APS-related complications is not clear. Based on encouraging case reports of AHSCT, we decided to offer this approach despite the considerable risks associated with the patient's kidney failure, frailty and a BMI of 17.3. The post-transplantation course was favourable and in line with previous reports [12, 13], with complete disappearance of APS-related antibodies and normalisation of C3 and a likely disappearance of LA. To our knowledge this is the first reported case of a successful lowering of aPS/PT after AHSCT. The patient remained without SLE or APS-related complications, with persistently negative relevant serology for more than 8 years post AHSCT and she had a successful kidney transplant in this time.

Discontinuation of anticoagulation was considered but treatment was continued after shared decision-making. Such an outcome of AHSCT for refractory ADs has been described as a "functional cure" of the disease [21], and while a relapse is certainly still possible, the effect of AHSCT was striking and potentially lifesaving, although causal attribution from a single case is not possible. Given the seemingly favourable balance between efficacy and harmful effects of AHSCT in selected patients with ADs, some have argued that this therapy should not be considered only as salvage therapy for very challenging cases but might be included earlier in the care of patients who do not respond well to standard therapy [22, 23].

Patient B was diagnostically challenging. His phenotype overlapped substantially with POEMS syndrome, but he did not meet conventional diagnostic criteria because polyneuropathy is mandatory and was absent [3]. We identified 2 major criteria (monoclonal plasma cell-proliferative disorder and CD) and 3 minor criteria (hepatomegaly, papilloedema, and thrombocytosis) of POEMS syndrome, while the bone lesions were osteolytic rather than sclerotic. Constitutional symptoms, inflammatory-marker elevation, anaemia, and the characteristic histology were consistent with the Castleman disease spectrum [24]. We therefore describe the condition as a POEMS syndrome-like clonal plasma cell disorder with features of

Castleman disease. Repeated kidney biopsies demonstrated progressive TMA. The monoclonal gammopathy was a plausible driver, although a direct pathogenic role of the MI could not be proven.

Cardiac involvement is not a common feature of POEMS syndrome or CD, although pericardial effusions and myocardial disease, including amyloidosis, have all been reported [25–28]. In Patient B this was the initial presentation of the disease and potentially the most harmful and life-threatening aspect, with progression to diffuse myocardial fibrosis. The precise aetiology of cardiac involvement in this case is not clear, but cardiac TMA and amyloidosis are two possibilities. We did not perform a cardiac biopsy so neither option could be confirmed. Amyloidosis seems less likely given that amyloid deposits were not found in any of the biopsies performed. TMA can be associated with adverse cardiovascular outcomes, such as heart failure, myocardial ischaemia, arrhythmias, and cardiogenic shock, as shown in different TMA-related diseases [29–31]. The cardiac MRI findings were similar to findings reported in other patients with POEMS and cardiac involvement, and the initial interpretation of myocarditis in the first MRI could have been signs of patchy myocardial ischaemia as these can be very similar [25, 32, 33].

The initial therapeutic response in Patient B was unsatisfactory. Ravulizumab had no clear clinical effect, and methylprednisolone plus rituximab improved the constitutional symptoms only transiently before treatment was changed to daratumumab, bortezomib, and lenalidomide after plasmacytoma was confirmed. There was no clear response to this regimen: the MI persisted, bone and retroclavicular lesions remained, kidney and cardiac disease progressed, and constitutional symptoms and inflammatory-marker elevation recurred. AHSCT was recommended to the patient based on reported outcomes in POEMS syndrome and Castleman disease [8, 9, 34]. Over 8 months after AHSCT, symptoms resolved, kidney function and blood pressure improved, proteinuria decreased, thrombocytosis resolved, anaemia improved, and inflammatory markers nearly normalised. The kidney improvement and the improvement in blood pressure control are consistent with reduced kidney TMA activity, however, because no repeat kidney biopsy was performed and systemic markers of TMA had remained normal throughout the disease, we have no definite proof of this conclusion. The longevity of this remission is unclear. One worrying feature is that in terms of lowering of MI, we did not achieve a complete or very good partial response, but only a partial response.

## Conclusions

These cases illustrate that organ injury in secondary TMA may progress despite a partial response to immunosuppressive or immunomodulatory treatment and without persistent conventional haematological evidence of active microangiopathy. In Patient A, serious cardiac and cerebrovascular events occurred after apparent control of the acute CAPS episode, whereas in Patient B biopsy-proven kidney TMA progressed despite consistently normal systemic markers of microangiopathic haemolysis. Cardiac involvement was clinically important in both patients, although its precise relationship to TMA could not be established. These observations emphasize that disease activity should be assessed not only through platelet count, LDH, haptoglobin and schistocytes, but also through the trajectory of the affected organs and the activity of the underlying systemic disorder. When the clinical course is

discordant with conventional laboratory markers, a low threshold for targeted cardiac or neurological reassessment may be appropriate; however, these cases cannot provide a recommendation for a routine surveillance protocol or the diagnostic performance of troponin or MRI.

The favourable outcomes observed in these and previously reported cases support further consideration of AHSCT as a treatment strategy for severe secondary TMA associated with a potentially transplant-responsive autoimmune or clonal disorder. Although AHSCT has generally been used after failure of conventional treatment, this reflects the circumstances in which it has been studied rather than evidence that it should necessarily be restricted to rescue therapy. Its optimal position in the treatment pathway remains unknown, including whether earlier intervention might prevent irreversible organ injury.

## Key clinical lessons

- Normal platelet count, LDH, haptoglobin and absence of schistocytes do not exclude organ-limited secondary TMA or continuing organ injury.
- Kidney function, proteinuria, blood pressure, disease-specific biomarkers and cardiac or neurological manifestations should be interpreted together rather than relying exclusively on systemic markers of microangiopathic haemolysis.
- When organ progression is suspected despite reassuring conventional markers, targeted cardiac or neurological evaluation should be considered. These cases cannot provide a recommendation for a routine surveillance protocol in asymptomatic patients.
- A partial response to complement inhibition or other systemic therapy should not automatically be interpreted as complete control of the underlying autoimmune or clonal process.
- This and previously reported experience support AHSCT as a plausible treatment option in such cases. Most published experience concerns severe, refractory disease, so confidence is greatest in that setting; however, the optimal timing is unknown. The available evidence neither establishes nor excludes a benefit from earlier use.

## Abbreviations

<sup>18</sup>F-FDG PET/CT

positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography

aCL

anticardiolipin antibodies

AD

autoimmune disease

ADAMTS13

a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13

AHSCT

autologous haematopoietic stem cell transplantation

ANA

antinuclear antibodies

anti-dsDNA

anti-double-stranded DNA antibodies

APS

antiphospholipid syndrome

aPS/PT

anti-phosphatidylserine/prothrombin antibodies

aPTT

activated partial thromboplastin time

ARDS

acute respiratory distress syndrome

AZA

azathioprine

$\beta$ -2-GPI

beta-2-glycoprotein antibodies

BMI

body mass index

C1q

complement component 1q

C3

complement component 3

C4

complement component 4

C5b9

membrane attack complex

CAPS

catastrophic antiphospholipid syndrome

CD

Castleman disease

CMV

cytomegalovirus

CRP

C-reactive protein

CsA

cyclosporine

CT

computed tomography

CYC

cyclophosphamide  
DON  
Department of Nephrology  
EBV  
Epstein-Barr virus  
ECU  
eculizumab  
eGFR  
estimated glomerular filtration rate  
GSCL  
global glomerulosclerosis  
HD  
haemodialysis  
HHV-8  
human herpesvirus 8  
HIV  
human immunodeficiency virus  
ICD  
implantable cardioverter-defibrillator  
ICU  
intensive care unit  
IFTA  
interstitial fibrosis and tubular atrophy  
IgG  
immunoglobulin G  
IL-6  
interleukin-6  
IVIG  
intravenous immunoglobulin  
LA  
lupus anticoagulant  
LDH  
lactate dehydrogenase  
LGE  
late gadolinium enhancement  
MALT  
mucosa-associated lymphoid tissue  
MG  
monoclonal gammopathy  
MI

monoclonal immunoglobulin  
MP  
methylprednisolone  
MRI  
magnetic resonance imaging  
POEMS  
polyneuropathy,organomegaly,endocrinopathy,monoclonal protein,and skin changes  
RTX  
rituximab  
SLE  
systemic lupus erythematosus  
TMA  
thrombotic microangiopathy  
UPCR  
urinary protein-to-creatinine ratio  
WHO  
World Health Organization.

## **Declarations**

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### **Author contributions**

AŠ conceptualization; AK and AŠ wrote the original draft; AK, AŠ and NK created the visualizations; ŽVH, MŠ, ŠB, NAR, AAR, NK, PR, NG, AA, and AŠ revised the text and provided corrections. All authors read and approved the final manuscript.

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### **Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Written informed consent was obtained from both patients for publication of their clinical details and images.

### **Availability of data and materials**

All data supporting the findings of this case series are included in the article and its supplementary information files. Additional patient-level data are not publicly available to protect patient confidentiality.

### **Disclosure on the use of artificial intelligence**

During preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with language editing. The authors reviewed and edited all generated content and take full responsibility for the final manuscript.

### **Competing interests**

The authors declare no competing interests.

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# Figures

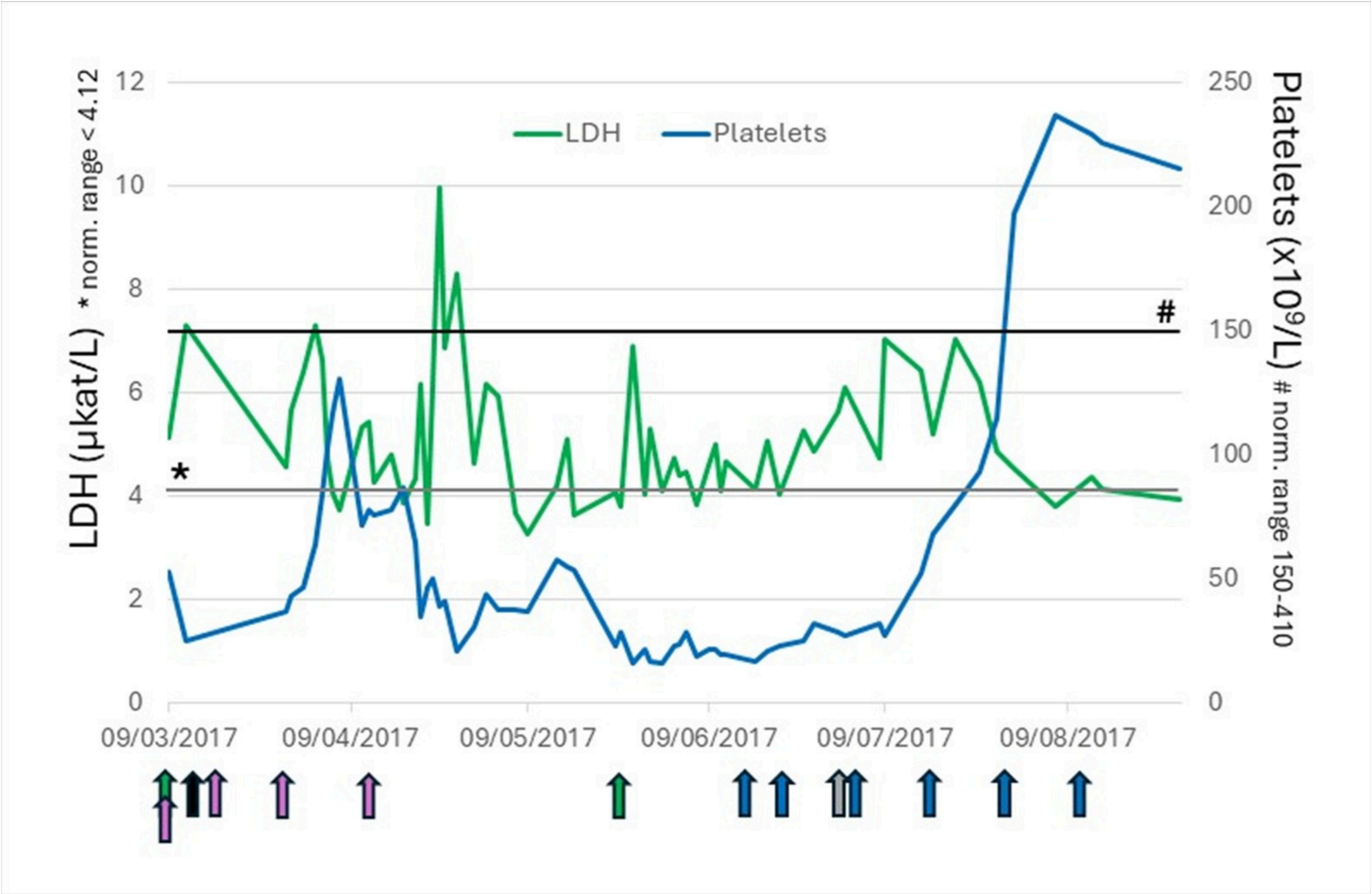


Figure 1

LDH and platelets in Patient A (hospitalization March - August 2017) with key therapy

Therapy: green arrows, pulse intravenous methylprednisolone; violet arrows, rituximab; black arrow, intravenous cyclophosphamide; blue arrows, eculizumab; grey arrow, start of cyclosporine.

Abbreviations: LDH, lactate dehydrogenase; norm., normal.

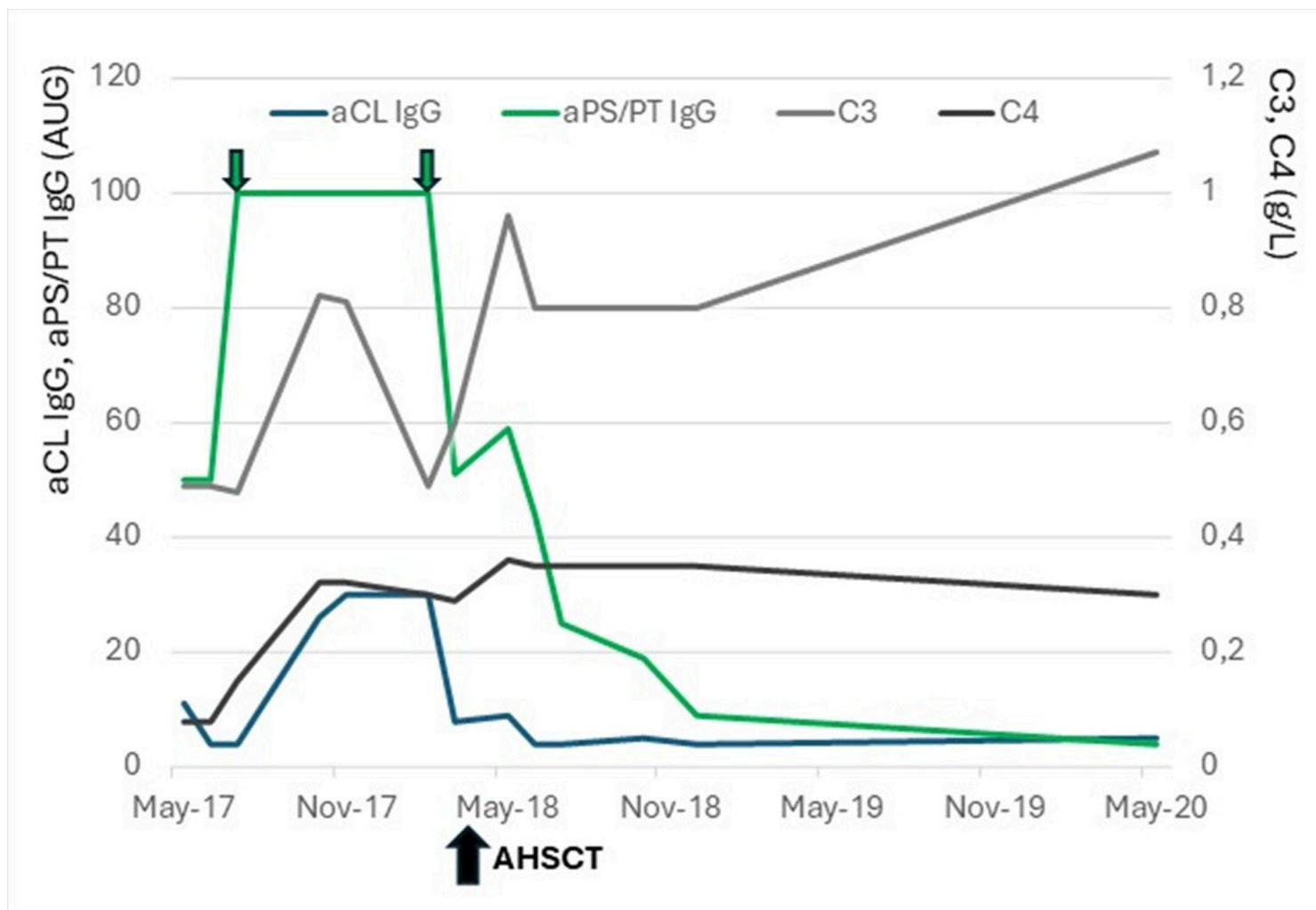


**Figure 2**

Levels of aCL IgG, aPS/PT IgG, C3, and C4 in Patient A prior to and after autologous haematopoietic stem cell transplantation

Arrows: green arrows, in the time between the arrows the aPS/PT IgG levels were reported as > 100, and the exact level was not precisely measured; black arrow, moment of AHSCT.

Abbreviations: aCL, anticardiolipin antibodies; AHSCT, autologous haematopoietic stem cell transplantation; aPS/PT, anti-phosphatidylserine/prothrombin antibodies; AUG, arbitrary units (standard units used to quantify aCL and aPS/PT antibodies in our laboratory); C3, complement component 3; C4, complement component 4; IgG, immunoglobulin G.

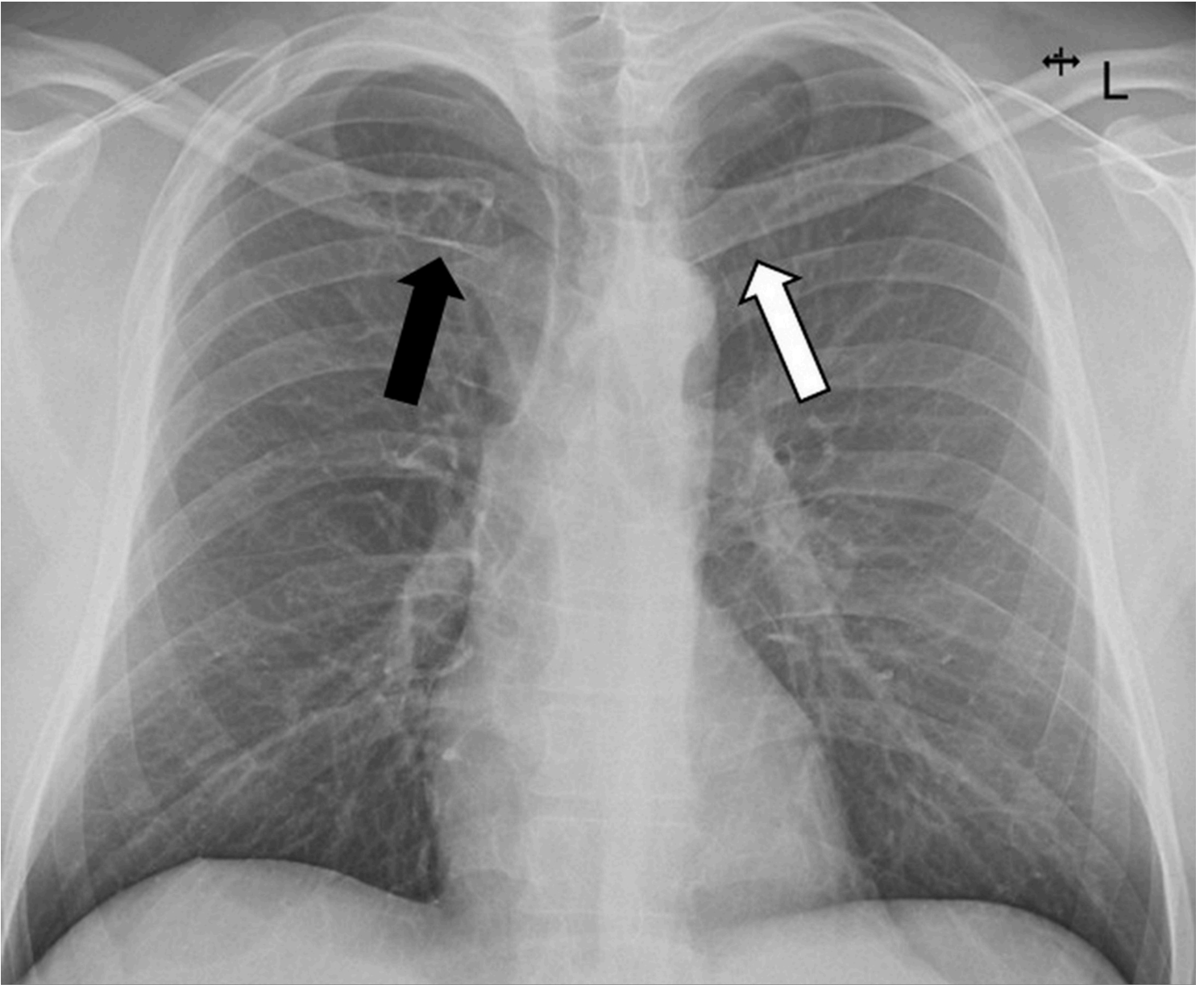


**Figure 3**

Chest radiograph of Patient B with osteolytic lesion in the right clavicle (black arrow) and healthy left clavicle (white arrow)

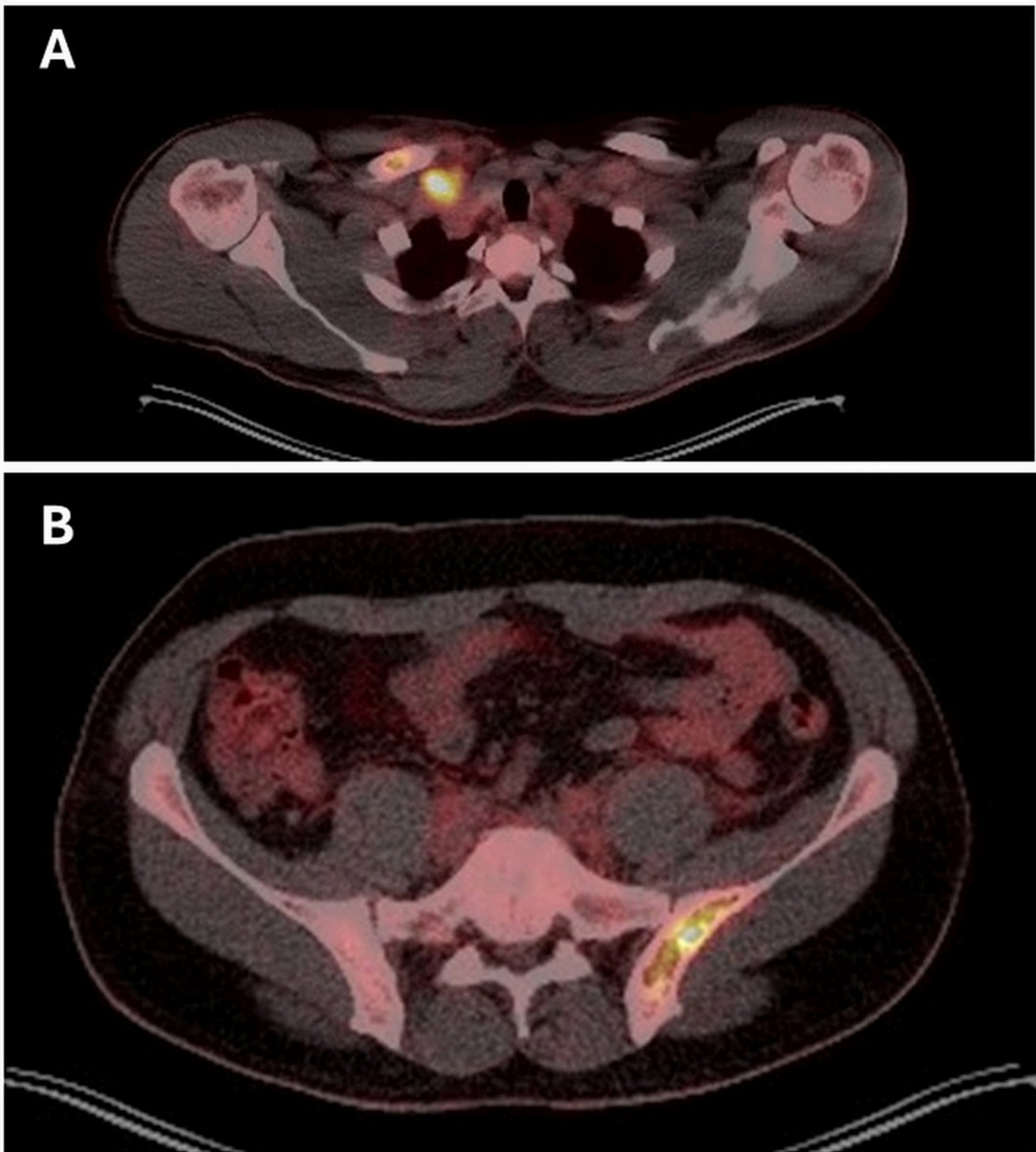


**Figure 4**

$^{18}\text{F}$ -FDG PET/CT scan in Patient B showing increased tracer uptake\* in the right clavicle and retroclavicular soft-tissue mass (A), and in the left iliac bone (B)

\* Increased tracer uptake can be identified by the yellowish-orange colour

Abbreviations:  $^{18}\text{F}$ -FDG, fluorine-18 fluorodeoxyglucose; CT, computed tomography; PET, positron emission tomography.

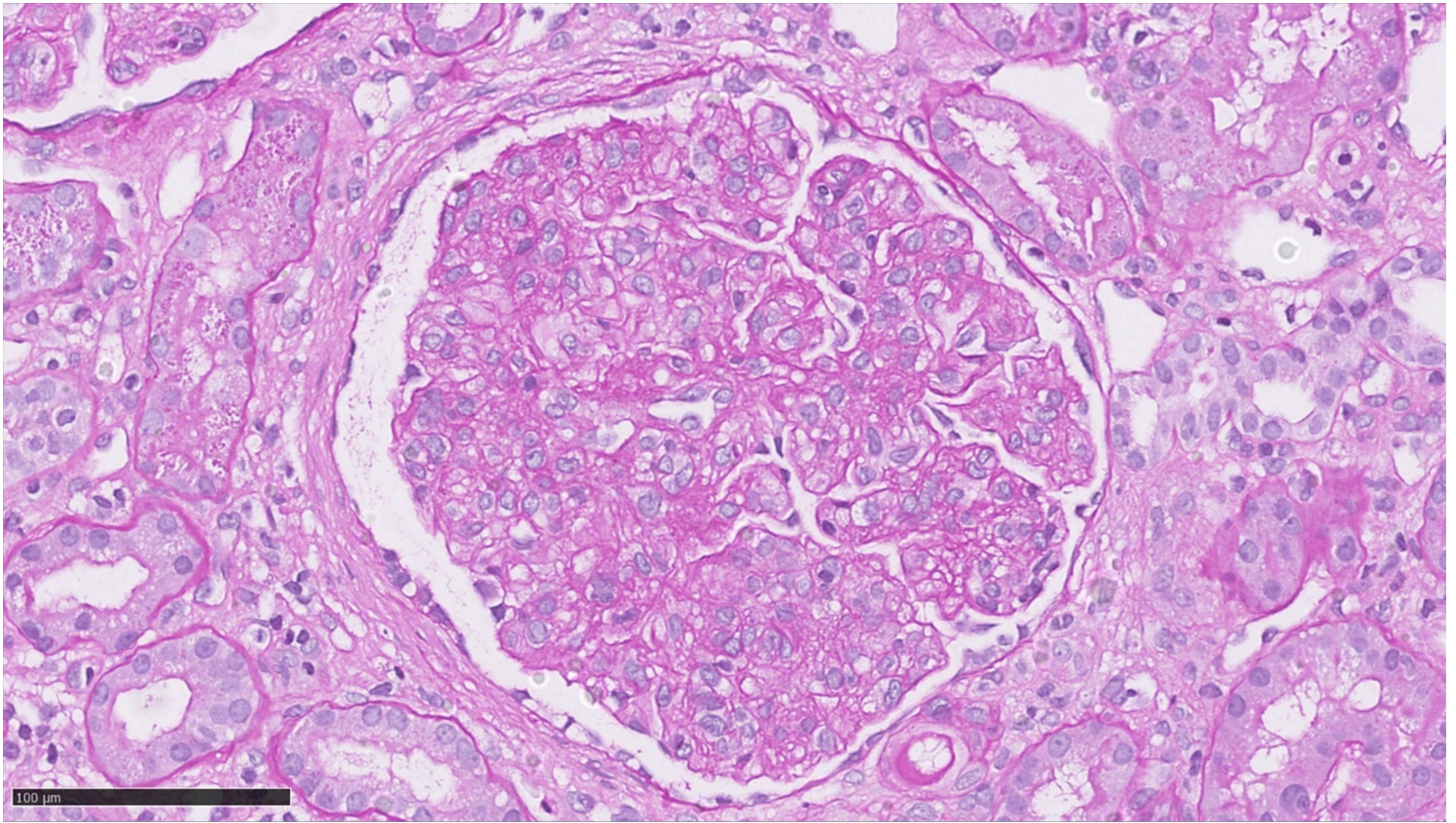


**Figure 5**

Kidney biopsy\* of Patient B showing extensive glomerular mesangiolysis with double contours of the glomerular basement membrane

\* Periodic acid–Schiff stain. Black line represents a length of 100 micrometres.

## Supplementary Files

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