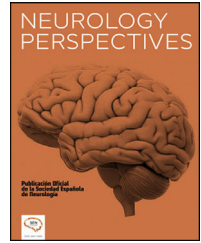




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SCIENTIFIC LETTER

Very late-onset membranous nephropathy secondary to alemtuzumab in a patient with multiple sclerosis

Nefropatía membranosa muy tardía secundaria a alemtuzumab en paciente con esclerosis múltiple

Z.F. Anabel^{a,*}, M.A. Gema^c, C.E. Bonaventura^b, P.R. Judith^c

^a Sección Neurología Hospital General de Castellón, Avinguda de Benicàssim, 128, 12004 Castelló de la Plana, Castelló, Spain

^b Servicio Neurología, Unidad de Esclerosis Múltiple, Hospital Universitario y Politécnico La Fe, Avinguda de Fernando Abril Martorell, 106, 46026 Valencia, Spain

^c Servicio Anatomía Patológica, Hospital Universitario y Politécnico La Fe, Avinguda de Fernando Abril Martorell, 106, 46026 Valencia, Spain

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Dear Editor:

Alemtuzumab causes autoimmune side effects in more than 30% of patients with multiple sclerosis between 3 and 4 years after the last dose, with cases of secondary autoimmune nephropathy being rare. We present a case of membranous nephropathy manifesting 63 months after the last dose of alemtuzumab, followed by immune thrombocytopenia and vitiligo, beyond the 48 months of follow-up established by regulatory agencies.

Our patient was a 55-year-old woman diagnosed 14 years earlier with relapsing–remitting multiple sclerosis (RRMS), based on MRI findings that met 4 Barkhof criteria, and the presence of IgG and IgM oligoclonal bands restricted to the CSF. She also presented hypertension, type 2 diabetes mellitus, and dyslipidaemia. The patient started treatment with interferon beta-1b (Extavia®), but after 3 years she presented a relapse with spinal symptoms, with new gadolinium-enhancing lesions and a poorer residual Expanded Disability Status Scale (EDSS) score (from 1.0 to 2.0). We added fingolimod, and the patient was included in

the EARLIMS study.¹ After 20 months of receiving fingolimod, she displayed a new gadolinium-enhancing lesion and EDSS score progressed to 2.5; alemtuzumab was indicated after a further relapse (first infusion in 2016).

At 2 years after onset of alemtuzumab, she presented somnolence and oedema and was diagnosed with autoimmune thyroiditis (anti-thyroid peroxidase antibodies >600 U/mL); treatment was started with levothyroxine. The patient remained stable for up to 5 years after alemtuzumab onset, when she presented sustained worsening in the EDSS score, which reached 4 in the absence of activity or inflammation; she was then diagnosed with secondary progressive multiple sclerosis.

During the last month of the patient safety programme (the 63rd month after alemtuzumab onset), a urine analysis revealed proteinuria (100 mg/kg). Given the suspicion of autoimmune kidney disease, the nephrology department performed a study that confirmed nephrotic proteinuria in several tests, with decreased blood protein levels, and kidney function within the normal range. A kidney biopsy (Figs. 1 and 2) yielded findings compatible with stage 3 membranous nephropathy and secondary membranous glomerulonephritis with positive IgG4 and negative PLA2R deposition. A study of secondary causes of autoimmune membranous nephropathy (autoimmunity, TC-TAP, PLA2R,

* Corresponding author at: Hospital General Universitario de Castellón. Avinguda de Benicàssim, 128, 12004 Castelló de la Plana, Castelló, Spain.

E-mail address: anabelzf95@gmail.com (Z.F. Anabel).

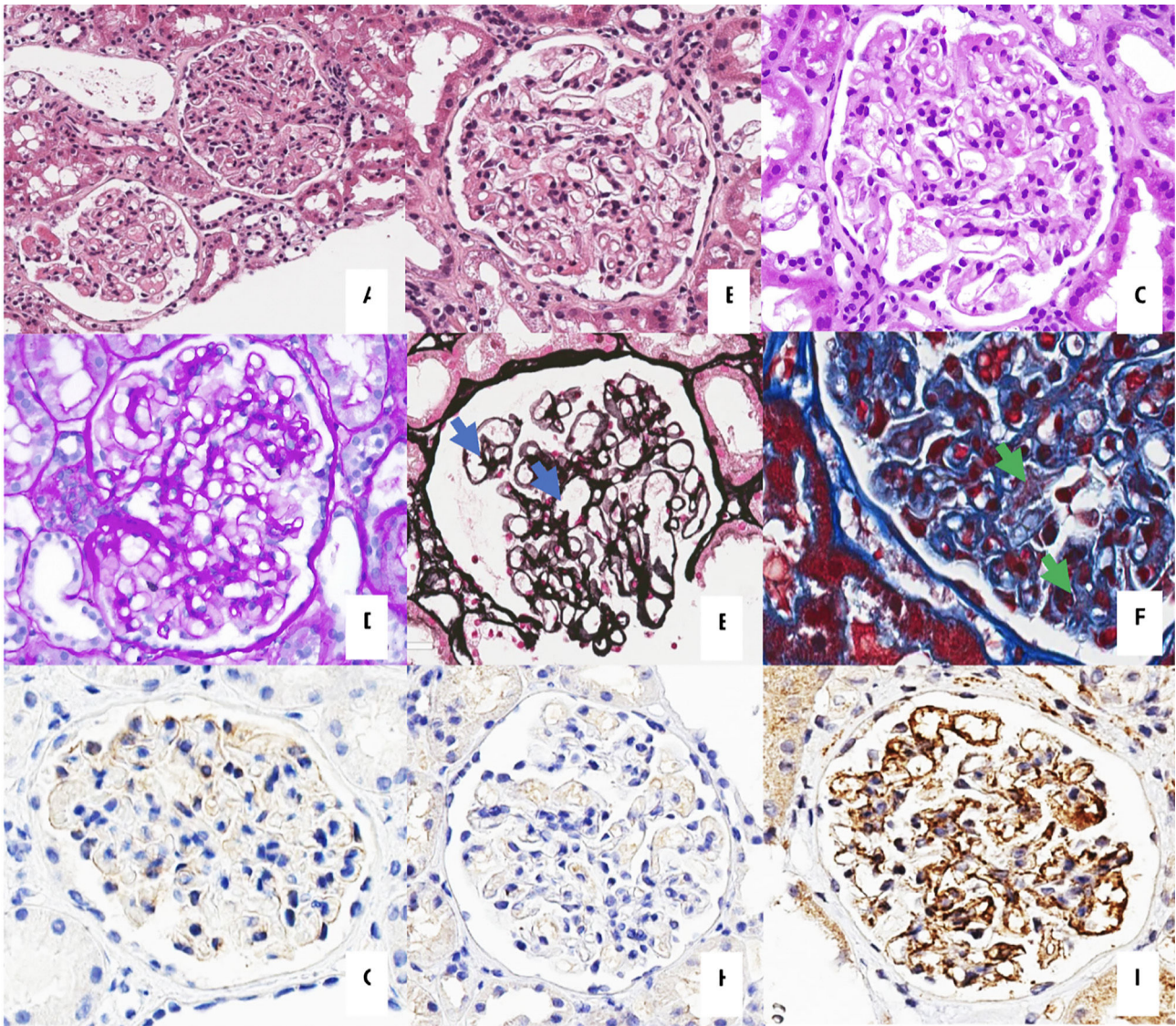


Fig. 1 (A–C) Haematoxylin-eosin staining, 20× (A) and 40× (B–C). The images display overall and diffuse thickening of the glomerular basement membrane (GBM), and focal and diffuse mesangial expansion. (D) Periodic acid–Schiff (PAS) stain, 40×. We identified mesangial expansion positive for PAS staining and GBM thickening. (E) Histochemical study with methenamine silver stain (Jones staining), 40×. This image shows the thickening of the GBM and the presence of focal spicules (blue arrow). (F) Masson's trichrome stain, 40×. This image shows the presence of subepithelial fucsinophilic deposits (green arrows). (G) PLA2R immunohistochemical staining, 40×. Absence of positivity. (H) IgG4 staining, 40×. Absence of positivity. (I) C4d staining, 40×. The image shows presence of overall and diffuse linear positivity at the GBM, as compared to C4d staining. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

etc) was performed. All results were negative, leading to diagnosis of membranous nephropathy secondary to alemtuzumab. The study of the kidney disease also revealed a decrease in platelet levels, compatible with mild immune thrombocytopenia secondary to alemtuzumab administration. The patient required no initial treatment until April 2023, when she showed a new (persistent) decrease in platelet levels, with titres below 50 000, requiring treatment with rituximab. Together with hypothyroidism, membranous nephropathy, and immune thrombocytopenia, she was also diagnosed with autoimmune vitiligo. Regarding kidney function, the patient presented a glomerular

filtration rate within the normal range, but proteinuria remained at 300 mg/dL and haematuria persisted (33 cells/ μ L); these alterations were mainly treated with antihypertensive drugs and diuretics.

Alemtuzumab is an effective monoclonal antibody against CD52 that is widely used in the treatment of aggressive multiple sclerosis. Limitations for its use include the development of autoimmune diseases, with thyroid disease being the most frequent. Other complications had been reported, including immune thrombocytopenia and several types of kidney disease. Such complications manifest between the first and third year after onset of alemtuzumab

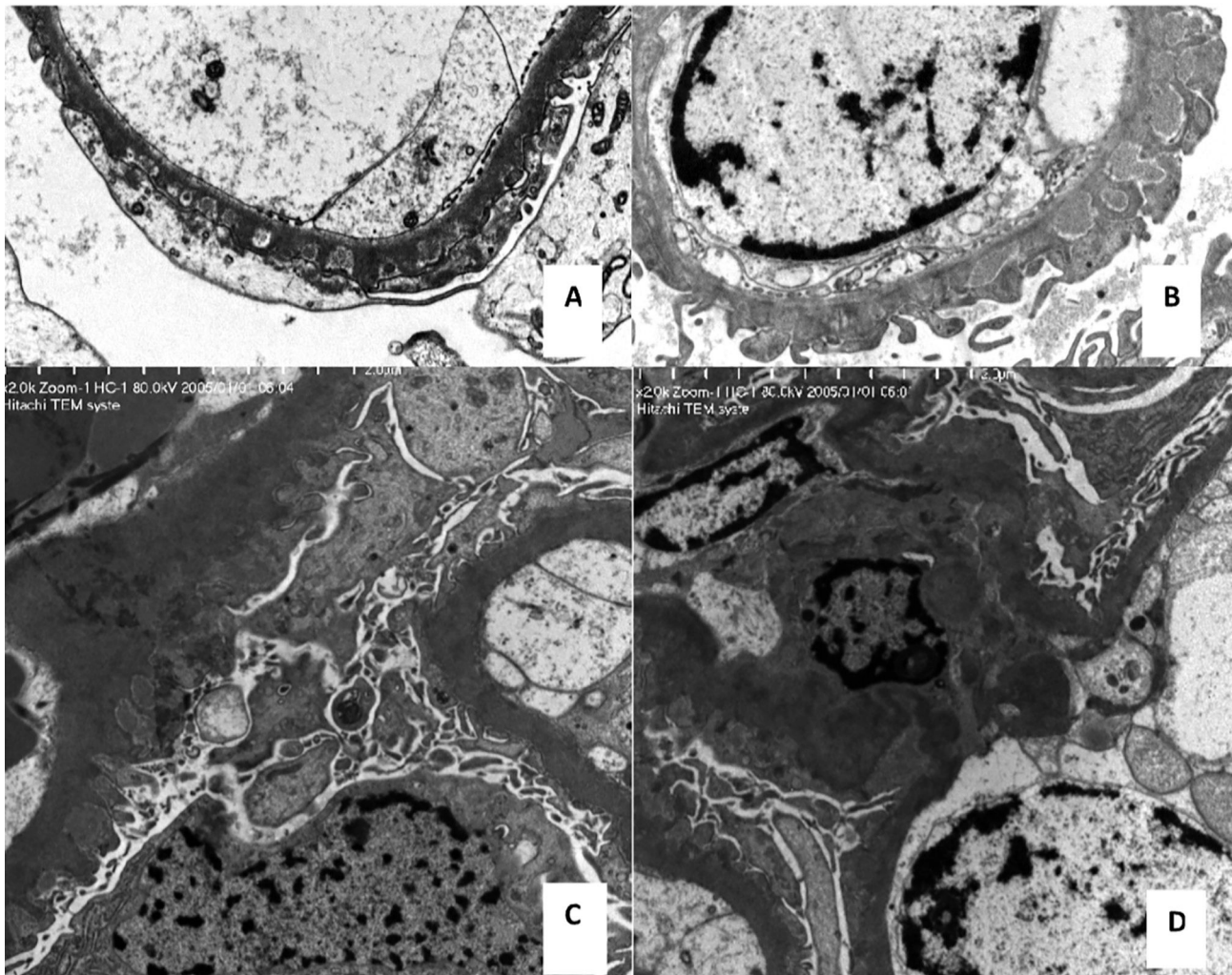


Fig. 2 (A–C) We observed mild thickening of the glomerular basement membrane and presence of electron-dense deposits, with areas of reabsorption (stage III membranous nephropathy). (D) Electron-dense mesangial and paramesangial deposits were identified; these, together with the immunohistochemical findings, are indicative of secondary membranous nephropathy.

administration. In the current patient safety programme, the clinical and laboratory follow-up period was extended to 4 years after the last dose of alemtuzumab, including blood and thyroid alterations and kidney function.^{2–4} Our patient presented 4 autoimmune events after infusion of alemtuzumab, 3 of which presented delayed onset, such as membranous nephropathy at 63 months after the first dose. This contrasts with 2 cases reported in a series of 16 patients with autoimmune kidney disease secondary to alemtuzumab that manifested earlier, at months 5 and 13 after treatment onset.⁵ Differential diagnosis of kidney disease secondary to alemtuzumab also includes anti-glomerular basement membrane disease and tubulointerstitial nephritis.² Our patient's progression was different to that observed in those 2 kidney diseases, and anatomical pathology findings were consistent with diagnosis of membranous nephropathy.⁵ The patient presented no previous autoimmunity, although this situation has been shown not to predispose to additional autoimmunity after treatment, according to a study of 96 patients.⁶

Regarding the management of membranous nephropathy, the guidelines followed in our case were described elsewhere. Treatment is based on angiotensin-converting enzyme inhibitors and diuretics, with all patients presenting favourable progression.⁵

Conclusions

Alemtuzumab is an anti-CD52 monoclonal antibody approved for the treatment of RRMS. Thanks to its action mechanism, it is highly effective, although adverse reactions have been described, including autoimmune disease.

Close follow-up over 6 years helps identify the majority of these effects, with thyroid diseases being the most frequent.

In our case, onset of autoimmune kidney disease occurred later, supporting the need to perform further clinical/laboratory tests and long-term studies of the effect of alemtuzumab on the immune system after immune reconstitution.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurop.2024.100148>.

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