Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients

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Co-presentation with both ANCA and anti-GBM antibodies is thought to be relatively rare. Current studies of such 'double-positive' cases report small numbers and variable outcomes. To study this further we retrospectively analyzed clinical features and long-term outcomes of a large cohort of 568 contemporary patients with ANCA-associated vasculitis, 41 patients with anti-GBM disease, and 37 double-positive patients with ANCA and anti-GBM disease from four European centers. Double-positive patients shared characteristics of ANCA-associated vasculitis (AAV), such as older age distribution and longer symptom duration before diagnosis, and features of anti-GBM disease, such as severe renal disease and high frequency of lung hemorrhage at presentation. Despite having more evidence of chronic injury on renal biopsy compared to patients with anti-GBM disease, double-positive patients had a greater tendency to recover from being dialysis-dependent after treatment and had intermediate long-term renal survival compared to the single-positive patients. However, overall patient survival was similar in all three groups. Predictors of poor patient survival included advanced age, severe renal failure, and lung hemorrhage at presentation. No single-positive anti-GBM patients experienced disease relapse, whereas approximately half of surviving patients with AAV and double-positive patients had recurrent disease during a median follow-up of 4.8 years. Thus, double-positive patients have a truly hybrid disease phenotype, requiring aggressive early treatment for anti-GBM disease, and careful long-term follow-up and consideration for maintenance immunosuppression for AAV. Since double-positivity appears common, further work is required to define the underlying mechanisms of this association and define optimum treatment strategies.

Anti-glomerular basement membrane (GBM) disease and the anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are rare conditions, with estimated incidences in Europe of 1 and 20 per million population per year, respectively.[1,2] The concurrence of both ANCA and anti-GBM antibodies in individual patients, however, is well-recognized, and occurs at a much higher frequency than would be expected by chance alone. This phenomenon was first reported within a few years of the first description of ANCA in the 1980s,[3,4] and has been observed in several series from around the world over the subsequent 30 years.[5–8] It is clear that the 2 antibody populations associated with these diseases are antigenically distinct,[9] and that this phenomenon is not due to cross-reactivity, although the mechanisms of the association are not fully understood.

Several studies have reported the outcomes of these patients who are double positive, although with conflicting findings; some have observed better outcomes compared with those with single-positive anti-GBM disease,[4,10,11] while others have suggested that patients who are double positive have comparable or worse outcomes.[5,6,12–16] These studies, however, have generally been limited by small size (many describing fewer than 20 cases) and variations in the severity of disease at presentation, with between 0% and 100% of patients being dependent on dialysis at diagnosis.[8,15] Furthermore, in the largest series to date, from Chinese centers, fewer than 25% of

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Table 1 | Case identification, demographics, clinical features, and serology

	AAV	Anti-GBM	Double positive	AAV versus DP versus GBM	AAV versus DP	GBM versus DP	AAV versus GBM
				P value			
Cases, *n*	568	41	37	–	–	–	–
• United Kingdom	171	19	20				
• Sweden	100	13	8				
• Czech Republic	297	9	9				
Cases, %	87.9%	6.3%	5.7%				
Demographics							
Age, yr (range)	62.3 (11–95)	58.3 (13–91)	63.6 (17–88)	0.17	0.99	0.31	0.21
Gender							
• Male	54%	46%	38%	0.11	0.06	0.49	0.34
• Female	46%	54%	62%				
Clinical Features							
Duration of symptoms,[a] wk (range)	12 (0–56)	2 (0–20)	10 (1–26)	**<0.01**	0.99	**<0.01**	**<0.01**
Lung hemorrhage	131/568 23%	16/41 40%	14/37 38%	**0.01**	**0.04**	0.85	**0.02**
Required RRT at presentation	132/568 23%	26/41 63%	21/37 57%	**<0.01**	**<0.01**	0.55	**<0.01**
eGFR,[b] ml/min (range)	29 (5–90)	20 (5–90)	19 (6–76)	0.06	0.11	0.99	0.67
Serum creatinine,[b] μmol/l (range)	186 (39–693)	275 (62–667)	309 (71–606)	0.06	0.18	0.99	0.37
Serology							
Anti-GBM level, xULN (range)	–	5.4 (1–29.1)	14.2 (1–50.4)		0.06		–
Proportion seronegative for anti-GBM, %	–	4/41 11%	4/37 11%		1.00		–
ANCA serology, %					**<0.01**	–	–
• Anti-MPO	48%		70%				
• Anti-PR3	51%		27%				
• Anti-MPO & PR3	<1% (*n* = 2)		3%				

AAV, anti-neutrophil cytoplasm antibody–associated vasculitis; DP, double-positive; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; MPO, myeloperoxidase; PR3, proteinase 3; RRT, renal replacement therapy; xULN, multiples of upper limit of normal.
Results expressed as median ± range. Comparison between groups by Kruskall–Wallis test with Dunn's post-test to ascertain differences between individual groups (for continuous data), or by chi-square test (for categorical data).
[a]Calculated for a sample of 48 ANCA cases.
[b]Censored for patients on RRT.

patients were treated with plasma exchange, and so the applicability of the findings to European patients treated with substantially different therapeutic regimens is limited.[7,16]

The aim of the present study is to describe the clinical features and long-term outcomes of a contemporary cohort of patients with double-positive ANCA and anti-GBM disease. Given the rarity of these patients, we have identified cases from 4 large Northern European nephrology centers, which employ comparable treatment protocols for these cases, including plasma exchange, cyclophosphamide, and steroids, unless contraindicated. We have compared clinical features and outcomes to those for single-positive AAV and single-positive anti-GBM disease. Because patients with double-positive disease more closely resemble those with single-positive anti-GBM disease at presentation, we have also compared histopathology and treatment in these 2 groups.

RESULTS
Case identification and demographics
Between 2000 and 2013, a total of 646 cases were identified at 4 centers in 3 countries, including 568 patients with

single-positive AAV, 41 with single-positive anti-GBM disease, and 37 patients who were double positive for anti-GBM antibodies and ANCA (hereafter AAV, anti-GBM, and double-positive groups, respectively) (Table 1). The ratio of double-positive to single-positive anti-GBM cases was similar in all 3 countries (47% overall); however, patients who were double positive represented a variable proportion of the AAV cases (3% to 10.5%; 6.1% overall). The demographic features of the cohort are summarized in Table 1. The single-positive anti-GBM group demonstrated the typical bimodal age distribution of this disease, whereas patients who were double positive had an age distribution similar to patients with isolated AAV (Figure 1). There was no significant difference in gender ratio between the 3 groups. Notably, 1 patient in the double-positive group had a previous diagnosis of isolated anti-myeloperoxidase (MPO) and AAV 2 years prior to presenting with double-positive disease.

Clinical presentation and serology
Table 1 summarizes key clinical features and serological findings at presentation. The duration of symptoms prior to receiving a diagnosis was similar in the AAV and