The Clinical and Immunologic Features of Patients With Combined Anti-GBM Disease and Castleman Disease

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Patients with both anti–glomerular basement membrane (anti-GBM) disease and Castleman disease have been rarely reported. In this study, we report 3 patients with this combination. They had immunologic features similar to patients with classic anti-GBM disease. Sera from the 3 patients recognized the noncollagenous (NC) domain of the α3 chain of type IV collagen (α3(IV)NC1) and its 2 major epitopes, EA and EB. All 4 immunogloblin G (IgG) subclasses against α3(IV)NC1 were detectable, with predominance of IgG1. In one patient with lymph node biopsy specimens available, sporadic plasma cells producing α3(IV)NC1-IgG were found, suggesting a causal relationship between the 2 diseases. One patient, who achieved remission with antibody clearance and normalization of serum creatinine and interleukin 6 concentrations after plasma exchange and 3 cycles of chemotherapy, experienced recurrence of anti-GBM antibodies and an increase in interleukin 6 concentration after chemotherapy discontinuation because of adverse effects, but both returned to normal after another cycle of chemotherapy. This clinical course and the pathologic findings support the hypothesis that the Castleman disease–associated tumor cells are the source of the anti-GBM autoantibodies.

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Introduction

Anti–glomerular basement membrane (anti-GBM) disease is a classic autoimmune disease with autoantibodies directed against the GBM, rapidly progressive glomerulonephritis, and alveolar hemorrhage.[1,2] The primary antigen targeted by anti-GBM autoantibodies is the noncollagenous (NC) domain of the α3 chain of type IV collagen (α3(IV)NC1),[3,4] which has 2 major conformational epitopes, EA and EB, involving amino acids 17 to 31 and 127 to 141, respectively.[5,6]

Castleman disease, a lymphoproliferative disorder, features hyperplastic lymph nodes characterized by follicular hyperplasia and capillary proliferation with endothelial hyperplasia.[7,8] Renal involvement, though not typical, has been reported by 2 large retrospective studies to occur in 25% to 54% of Castleman disease cases.[9,10]

Anti-GBM disease combined with Castleman disease is rare. To our knowledge, there has only been 1 case reported, by Lv et al.[11] The co-occurrence of Castleman disease with various autoantibodies has been reported sporadically.[12-16] A role of B cells from Castleman tumors in the production of the antibodies against epidermal protein and the pathogenesis of paraneoplastic pemphigus has been reported,[13] but whether anti-GBM antibodies could come from Castleman tumors remains unclear, as are the immunologic characteristics of these antibodies. In the present study, we investigated the clinical and immunologic features of 3 patients with combined anti-GBM disease and Castleman disease, aiming to gain further information regarding the pathogenesis of this rare entity.

Case Reports

Case 1

A 38-year-old man was referred to our hospital with a 20-day history of fever and gross hematuria. Physical examination showed swollen lymph nodes in the neck and supraclavicular fossa. Serum creatinine concentration was 369 μmol/L at presentation (estimated glomerular filtration rate [eGFR], 17.1 mL/min/1.73 m^2 [information for the estimating equation used and other detailed methods are provided in Item S1]) and then rapidly increased to 693 μmol/L (eGFR, 8.3 mL/min/1.73 m^2) with oliguria. A test for circulating anti-GBM antibody gave positive results (titer > 200 RU/mL; Table 1).

Two years prior, the patient had been found to have swollen lymph nodes in his neck, axilla, supraclavicular fossa, and the inguinal region. A diagnosis of multicentric Castleman disease, mixed subtype, was made based on a lymph node biopsy (Fig 1A). Serum creatinine concentration was elevated (152 μmol/L; eGFR, 48 mL/min/1.73 m^2), but anti-GBM antibody was not detected. He was treated with 4 cycles of COP (cyclophosphamide, vincristine, and prednisone) chemotherapy, after which the lymph nodes became impalpable and serum creatinine concentration decreased to a normal level.

On the most recent admission, anti-GBM disease and a relapse of Castleman disease was diagnosed. The patient was treated with plasma exchange, methylprednisolone pulse therapy, and 1 cycle of R(ituximab)-COP therapy. Despite the aggressive treatment, anti-GBM antibody titer was still high (114 RU/mL) and the patient progressed rapidly to end-stage kidney disease and became dialysis dependent.

Sera from this patient was found to recognize the (IV)NC1 domains of all 5 α chains that are found in the human GBM and all 3 α3(IV)NC1 epitopes (EA, EB, and non-EA/EB). In terms of circulating immunoglobulin G (IgG) against α3(IV)NC1, all 4 subclasses were detected, with dominance of IgG1 (Table 1; Fig S1).

To investigate whether the anti-GBM antibodies were secreted from plasma cells in the swollen lymph nodes associated with Castleman disease, we used a tagged

Table 1. Demographic and Clinical Features of Patients With Anti-GBM Disease Combined With Castleman Disease

	Patient 1	Patient 2	Patient 3
Sex/age, y	M/38	M/56	M/32
Interval between lymph node swelling and onset of anti-GBM disease, mo	24	24	7
Smoking (Y/N)	N	N	Y
Hydrocarbon exposure (Y/N)	N	N	N
Prodromal infection (Y/N)	Y	N	Y
Hemoptysis (Y/N)	N	N	N
Gross hematuria (Y/N)	Y	Y	Y
Oliguria/anuria (Y/N)	Y	N	N
Urinary protein, g/24 h	—	5.7	4.1
Nephrotic syndrome (Y/N)	—	Y	Y
Albumin, g/L	35.3	26.7	29.7
Serum creatinine, μmol/L	693	598	391
ANCA (Y/N)	N	N	N
Serum anti-PLA_2R antibody (Y/N)	N	N	N
Serum anti-THSD7A antibody (Y/N)	N	N	N
Serum anti-GBM antibodies, RU/mL	>200	167	164
Crescents, %	—	90.0	59.1
Castleman histologic subtype	Mixed	Plasmacytic	Plasmacytic
Serum anti-HIV antibody (Y/N)	N	N	N
Plasma IL-6, pg/mL (ref range, 108.8 ± 41.4)	—	196.0	401.8
Plasma IgG, g/L (ref range, 7.23-16.85)	8.9	10.0	16.2
Plasma IgA, g/L (ref range, 0.69-3.82)	1.2	3.3	1.4
Plasma IgM, g/L (ref range, 0.63-2.77)	0.7	0.4	1.5
Plasma C3, g/L (ref range, 0.6-1.5 g/L)	1.4	0.9	0.9
Plasma C4, g/L (ref range, 0.12-0.36)	0.3	0.2	0.3
Anti-α1(IV)NC1 antibody (ref range, <0.04)	1.39	0.90	0.20
Anti-α2(IV)NC1 antibody (ref range, <0.03)	0.85	0.51	0.06
Anti-α3(IV)NC1 antibody (ref range, <0.05)	1.37	0.87	0.56
Anti-α4(IV)NC1 antibody (ref range, <0.05)	0.25	0.27	0.03
Anti-α5(IV)NC1 antibody (ref range, <0.04)	0.94	0.46	0.02
Anti-EA antibody (ref range, <0.05)	1.08	0.73	0.81
Anti-EB antibody (ref range, <0.07)	1.13	0.73	0.50
Anti–non-EA/EB antibody (ref range, <0.04)	0.30	0.01	0.01
Anti-α3(IV)NC1 IgG1 (ref range, <0.01)	2.46	2.37	2.34
Anti-α3(IV)NC1 IgG2 (ref range, <0.01)	1.35	0.68	0.70
Anti-α3(IV)NC1 IgG3 (ref range, <0.002)	1.79	0.72	0.60
Anti-α3(IV)NC1 IgG4 (ref range, <0.01)	1.03	0.59	1.68
Treatment	PE+R-COP	PE+R-CHOP	PE+COP

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; COP, cyclophosphamide, vincristine, and prednisone; GBM, glomerular basement membrane; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IL-6, interleukin 6; N, no; PE, plasma exchange; PLA_2R, M-type phospholipase A_2 receptor; R-CHOP, rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisone; R-COP, rituximab, cyclophosphamide, vincristine, and prednisone; ref, reference; THSD7A, thrombospondin type-I domain-containing 7A; Y, yes.

recombinant α3(IV)NC1 as a probe against a lymph node biopsy specimen (see Item S1 for detailed methods). Sporadic IgG-secreting plasma cells producing antibodies reactive with α3(IV)NC1 were detected (Fig S2C). The mean number of reactive cells per high-power field (original magnification, ×400) was 13.8 ± 2.9 (standard deviation), whereas none were found in lymph nodes from a patient with Castleman disease but without anti-GBM disease (Fig S2I). No IgG4-secreting plasma cell was found in the lymph node, arguing against the possibility of IgG4-related disease in this patient (Fig S3).

Case 2

A 56-year-old man was admitted to the hospital with tea-colored foamy urine, which developed 1 week after antibiotic treatment for a cough and fever of 20 days' duration. Urinary protein excretion was 2.4 g/d. Blood tests showed serum albumin concentration of 23.4 g/L and serum creatinine concentration of 223.9 μmol/L (eGFR, 28 mL/min/1.73 m^2). A kidney biopsy was performed and revealed crescentic glomerulonephritis and membranous nephropathy (Fig 1D-F). After treatment with methylprednisolone and cyclophosphamide, serum creatinine concentration increased to 400.8 μmol/L (eGFR,