Lymphoproliferative disease and acquired C1 inhibitor deficiency

Angioedema due to acquired deficiency of the C1-inhibitor is a bridging condition between autoimmunity and lymphoproliferation. We report 32 patients with acquired C1 inhibitor deficiency: 23 have anti C1-inhibitor autoantibodies; 13 have monoclonal gammopathies of unknown significance and 9 have non-Hodgkin's lymphoma. Our series suggest that different forms of B cell disorders coexist and/or evolve into each other in acquired angioedema.

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Angioedema due to the acquired deficiency of the inhibitor of the first component of human complement (CI-INH) is a rare syndrome usually identified as acquired angioedema (AAE). One hundred and thirty-six cases are described literature.[1-3] The clinical features of C1-INH deficiency, which can also be of genetic origin (hereditary angioedema, HAE), includes subcutaneous, non-pruritic swelling without accompanying urticaria, involvement of the upper respiratory tract, and partial obstruction of the gastrointestinal tract presenting as abdominal pain. Unlike HAE, AAE has no family history of angioedema, but is characterized by a

Table 1. Characteristics of 32 patients with acquired deficiency of C1 inhibitors.

n	*Sex*	*Present age (years)*	*Age at diagnosis (years)*	*Age at onset (years)*	*Length of follow up (years)*	*Disease at onset*	*Disease at follow-up*	*Anti C1-INH*	*Monoclonal component*
1	M	86	72	72	10	No associate disease	No associate disease	Ig G k	none
2	M	78	60	57	16	No associate disease	No associate disease	Ig G k	none
3	M	62	58	58	4	No associate disease	No associate disease	Ig G k	none
4	F	58	47	40	11	No associate disease	No associate disease	IgAk	none
5	F	65	56	56	1	No associate disease	No associate disease	IgM	none
6	F	57	53	54	2	No associate disease	No associate disease	IgG	none
7	F	57	56	49	1	No associate disease	No associate disease	none	none
8	F	75	74	74	1	No associate disease	No associate disease	none	none
9	M	84	70	67	14	No associate disease	MGUS	IgMκλ	Ig M k
10	F	69	57	56	12	MGUS	MGUS	IgG λ	IgG λ
11	M	83	72	62	11	MGUS	MGUS	IgG λ	IgG λ
12	F	84	79	74	8	No associate disease	MGUS	IgM λ	IgG λ
13	M	50	42	39	8	MGUS	MGUS	IgM/IgGλ	IgG λ
14	M	53	44	44	9	MGUS	MGUS	Ig A λ	IgG λ
15	F	dead	48	40	24	Hydatidosis	MGUS	Ig G k	Ig G k
16	M	61	51	51	4	MGUS	MGUS	Ig M k	Ig M k
17	F	82	73	71	9	MGUS	MGUS	none	IgG K
18	F	60	55	50	5	No associate disease	MGUS	none	IgG λ
19	F	52	48	43	4	MGUS	MGUS	none	IgG λ
20	F	60	59	53	1	MGUS	MGUS	none	IgM k
21	M	69	55	53	14	No associate disease	MGUS	IgA λ	Ig A λ
22	F	69	58	57	11	No associate disease	Large B cell Lymphoma	IgM	none
23	M	dead	53	52	12	No associate disease	Lymphoplasmotic lymphoma	Ig G k	Ig M k
24	M	dead	63	63	15	Mantle cell lymphoma	Large B cell Lymphoma	none	
25	F	81	76	75	5	Lymphocytic lymphoma	Lymphocytic lymphoma	none	none
26	M	dead	55	55	24	No associate disease	Lymphoplasmotic lymphoma	IgM λ	πg M λ
27	F	67	65	60	2	Splenic marginal zone lymphoma	Splenic marginal zone lymphoma	IgM	IgM k
28	F	81	78	66	3	lymphoplasmacytoid lymphoma Waldeström's disease	lymphoplasmacytoid lymphoma/ Waldeström's disease	Ig M	IgM k
29	F	48	45	45	3	Nodal marginal zone lymphoma	Nodal marginal zone lymphoma	IgM	none
30	F	76	72	71	4	Follicular lymphoma	Follicular lymphoma	none	
31	F	82	81	76	1	No associate disease	Urinary bladder cancer	IgM k	none
32	F	dead	65	63	12	No associate disease	Breast cancer	IgA λ	none

MGUS: monoclonal gammopathy unknown significance; anti C1-INH: autoantibodies anti C1-inhibitor.

late onset of symptoms and a variable response to treatment due to the hyper catabolism of C1-INH. AAE is frequently associated with lymphoproliferative diseases and/or anti-C1-INH inactivating autoantibodies.

Lymphoprolipherative disorders described in AAE patients range from monoclonal gammopathies of uncertain significance (MGUS) to non Hodgkin's lymphoma (NHL). A pathogenic autoantibody can also indicate a breakdown in B cell proliferation control. Evidence that M components detected in these patients frequently correspond to the anti-C1-INH antibodies[4] and that patients with autoantibodies may develop lymphomas suggests that a single B cell clonal disorder, with different potential clinical evolutions, underlies all AAE.

This study aimed to clarify the relationship between the different forms of B cell proliferation present in AAE. Thirty-two patients were included, 23 of whom had been described elsewhere.[3] Patients were followed for a median of 8 years (range: 1-24). C1-INH activity was measured with a chromogenic assay (Technochrome C1-INH, Technoclone GmbH, Vienna, Austria), antigenic measurements of C1-INH, C4 and C1q were performed by radial immunodiffusion (NOR-Partigen and [for C1q] LC-Partigen, Behring, Marburg, Germany), autoantibodies to C1-Inhibitor were detected by ELISA.[4] Thirteen of 32 AAE patients (40%) fulfilled the diagnostic criteria for MGUS. According to a previous report[5] MGUS and autoantibodies to C1-INH shared the same heavy and light chain isotypes in 9 patients.

Nine patients (28%) presented NHL. Based on WHO classification, 7 patients had indolent lymphoma (3 lymphoplasmacytoid lymphoma/Waldeström disease, 1 small lymphocytic lymphoma, 1 splenic marginal zone lymphoma, 1 nodal marginal zone B cells lymphoma) and 2 had high-grade malignant lymphoma (1 large B cell lymphoma and 1 mantle cell lymphoma with progression to large B cell lymphoma). All patients with indolent lymphoma had advanced stage with bone marrow infiltration. Follicular lymphoma, the most frequent istotype of indolent lymphoma, was only found in one patient. This agrees with other series of patients in which indolent lymphoma were described in the setting of autoimmune disorders.[6-7]

In 7 out of 9 patients, NHL was diagnosed at the onset of angioedema or developed thereafter after a minimum of 3 months to a maximum of 7 years. In 2 patients NHL was already present, but not treated, when angioedema appeared, after 6 years and 3 months respectively.

Three patients received standard chemotherapy (CEOP: cyclophosphamide-vincristine and prednisone). One also received Rituximab and another received CEOP and subsequently fludarabine and cyclofosphamide for abdominal relapse. This last patient is still in complete remission after 6 years of follow up, while the other two died from lymphoma progression. One patient, with splenic marginal zone lymphoma, received splenectomy and no chemotherapy, and is in remission after 4 years of follow up. In the remaining 5 patients the disease is stable without therapy. Levi *et al.*[8] recently reported the remission of C1-INH induced acquired angioedema following Rituximab treatment. In our study, the three patients who received chemotherapy remained asymptomatic after treatment.

Table 2. Complement parameters in two patients with AAE and lymphoplasmacytoid lymphoma/Waldeström disease (patient #28) and follicular lymphoma (patient #30) treated with chemotherapy.

	C1-INH activity (%)	*C1-INH Ag (%)*	*C4 (%)*	*C1q (%)*	*Anti-C1-INH (UI/mL)*
Patient #28					
Baseline	< 5	31	<5	Na	500
After CYC	74	107	142	107	10
Waldenström diagnosis	< 5	38	<5	120	Na
After R-CHOP	116	115	143	86	60
Patient #30					
Baseline	<1	<1	<5	27	0
After treatment for NHL (fludarabine and CyC)	39	35	13	44	0
Remission	90	109	7	100	0

AAE: acquired angioedema; C1 INH: C1 inhibitor; Anti C1-INH: autoantibodies anti C1- inhibitor; CYC: cyclophosphamide; R-CHOP: rituximab-cyclophosphamide-vincristine and prednisone; Na: not available; NHL: non Hodgkin's lymphoma.

Monitoring of complement parameters in two of them showed reversal of the biochemical abnormalities (Table 2). Overall, these data are consistent with the hypothesis that pathological B cell clones are responsible for acquired C1-INH deficiency.

Ten patients had no apparent hematologic disease at diagnosis or during follow up. Eight of them had anti-C1-INH autoantibodies and two had autoantibodies and a non-hematological malignancy.

According to the data of the Italian cancer registry, the incidence of NHL is 114:100,000. This report confirms that the risk of NHL is markedly increased in patients with AAE. The variety of clinical presentations and response to therapy of NHL suggest that the course of B cell malignancies in these patients has no specific characteristics. The same seems to be true for MGUS, which does not progress to multiple myeloma with increased frequency. Finally, the coexistence in AAE patients of true B cell malignancy, non malignant B cell proliferation and pathogenic autoimmune responses suggest that etiopathogenesis of AAE is dominated by an altered control of B cell proliferation. Thus patients with AAE should be closely monitored for signs of lymphoprolipherative disease.

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