

High prevalence of splenic marginal zone lymphoma among patients with acquired C1 inhibitor deficiency

Roberto Castelli,¹ Maddalena Alessandra Wu,¹ Massimo Arquati,¹ Andrea Zanichelli,¹ Chiara Suffritti,¹ Davide Rossi² and Marco Cicardi¹

¹Department of Biomedical and Clinical Sciences Luigi Sacco, Luigi Sacco Hospital Milan, University of Milan, Milan, and ²Division of Haematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy

Received 22 September 2015; accepted for publication 9 November 2015

Correspondence: Roberto Castelli, Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milan, Luigi Sacco Hospital Milan, Milan, Italy.
E-mail: roberto.castelli@unimi.it

Summary

Marginal zone lymphoma represents about 10% of all non-Hodgkin lymphomas (NHLs). 33% of patients with acquired angioedema (AAE) due to acquired C1-inhibitor (C1-INH) deficiency (C1-INH-AAE) have or will develop NHLs. C1-INH-AAE is a rare condition. We report the follow-up of 72 C1-INH-AAE patients, followed for a median of 15 years (range 1–24). Median age was 71 (range 64–79) years; median age at onset of angioedema symptoms was 57.5 (range 50–66) years and it was 63 [range 45–80] years at diagnosis. Twenty patients were diagnosed with low-grade non-follicular B-cell lymphomas (75% were splenic MZL), one with follicular and three with high-grade lymphomas (two diffuse large B-cell lymphomas and one mantle cell lymphoma). Fifteen NHLs were diagnosed at onset of AAE or thereafter (3 months to 7 years), eight had already been diagnosed at onset of angioedema. Two of 24 patients remain on watchful wait. Thirteen of 24 received chemotherapy, two received rituximab. Three underwent splenectomy. All 18 patients receiving therapy for NHL experienced post-treatment reduction in AAE symptoms. Our study suggests that clonal B-cell proliferation is the pathology underlying AAE leading to production of C1-INH-neutralizing autoantibodies and to NHLs. The post-germinal centre origin of NHL suggests that immune stimulation may contribute to lymphomagenesis.

Keywords: acquired angioedema, Non Hodgkin Lymphoma, indolent non-follicular NHL, Splenic marginal zone lymphomas, antigen-driven lymphomagenesis.

Angioedema due to an acquired deficiency of the inhibitor of the first component of complement (C1-INH) is a rare syndrome usually identified as acquired angioedema (AAE). The clinical features of C1-INH deficiency, which can also be of genetic origin (hereditary angioedema, HAE), include recurrent, self-limiting local swellings involving the upper respiratory tract and the gastrointestinal tract with severe abdominal pain (Zingale *et al*, 2006). Swelling is due to local accumulation of bradykinin released from high molecular weight kininogen upon uncontrolled activation of plasma kallikrein deprived of its major physiological inhibitor, C1-INH (Cugno *et al*, 2009). The precise aetiology of acquired C1-INH deficiency remains undefined, but the majority of patients have an underlying B-cell disorder, which appears to be the crucial underlying pathology driving the consumption of C1-INH. These B-cell disorders range from production of anti-C1-INH autoantibodies to mon-

oclonal gammopathies of uncertain significance (MGUS) to Non-Hodgkin Lymphomas (NHLs) (Cicardi *et al*, 1996, 2003; Castelli *et al*, 2007; Branellec *et al*, 2012; Lam *et al*, 2012). The low levels of C1-INH due to its consumption by pathological lymphatic tissue or its autoantibody-mediated inactivation are associated with hyper-activation of the complement or contact system, which may further consume C1-INH. Standard treatment for AAE attacks is replacement therapy with plasma-derived C1-INH concentrate (pdC1-INH). However, some patients with AAE become progressively less responsive to pdC1-INH treatment (Cicardi *et al*, 1996; Castelli *et al*, 2007), possibly due to anti-C1-INH autoantibody development.

Growing experimental evidence suggests that microenvironmental interactions driven by inflammatory and infectious conditions favour the development or promotion of specific subtypes of indolent non-follicular NHLs (marginal zone

lymphomas, MZLs; lymphoplasmacytic lymphomas, LPLs; small lymphocytic lymphomas, SLLs). This evidence suggests a role for chronic immune stimulation, either from persistent microbial infections or from autoantigens, in B cell transformation (Wotherspoon *et al*, 1991; Franklin *et al*, 2006).

Further insight on the association between autoimmune disorders, antigen stimulation and NHL subtypes may help in understanding the underlying biology of antigen-driven lymphomagenesis, both in general and specific settings. Here we report data from our cohort of 72 AAE patients with a 33% rate of lymphoproliferative diseases. Most of them are indolent non-follicular B cell lymphoproliferative disease (INFBCLs,) suggesting a likely antigen-driven pathogenetic mechanism.

Patients and methods

Seventy-two AAE patients were included, 32 of which have already been described (Castelli *et al*, 2007). The diagnosis was based on a history of recurrent angioedema without urticaria, which began during or after the fourth decade of life, absence of family history of angioedema, and plasma levels of C1-INH function below 50% of normal. Median age at onset of angioedema symptoms was 57.5 (range 50–66) years and diagnosis was made at a median age of 63 (range 55–72) years. Fifteen of 24 (62.5%) were diagnosed at onset of AAE or thereafter (3 months to 7 years). Face oedema was the most frequent location reported by 83% of patients; 69% of patients reported peripheral/abdominal attacks and 58% reported oral mucosa and/or glottis attacks. Seventy nine per cent of patients had their acute attacks treated with one of the specific treatments: 86% used pdC1-INH, 46% used Icatibant. C1-INH-auto antibodies were detected in 71% of patients that used pdC1-INH; 24% of these patients became non-responsive to pdC1-INH and switched to Icatibant. Twenty-four of these patients had histologically confirmed diagnosis of NHL according to the WHO classification (Swerdlow *et al*, 2008) Patients were followed for a median of 15 years (range: 1–24). The following clinical data were collected from the medical records: patient demographics, complete blood cell counts, plasma lactic dehydrogenase (LDH) level, hepatitis B virus (HBV) and hepatitis C virus (HCV) serology, Ann Arbor Stage, International Prognostic Index (IPI), Follicular Lymphoma IPI (FLIPI), bone marrow findings, the presence of B symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, date of diagnosis, type of treatment, treatment response, date of relapse, date of last follow-up and cause of death and AAE status after lymphoma treatment.

Complement parameters were determined on serum or plasma samples stored at -80°C until tested. C1-INH, C4, C3 and C1q antigens were measured by radial immunodiffusion (Nor Partigen, Low Partigen for C1q Behring, Marburg, Germany). C1-INH antigenic and C4 were quantified using radial immunodiffusion or nephelometry; C1-INH function

was measured using a chromogenic or an immunoenzymatic assay. Results were normalized as a percentage of normal value (functional C1-INH normal range 70–130%; antigenic C1-INH normal range 70–115%; antigenic C4 normal range 60–140%). Autoantibodies to C1-INH in serum were measured by enzyme-linked immunosorbent assay (ELISA) using the method described by Alsenz *et al* (1987) with slight modifications (Alsenz *et al*, 1987; Cicardi *et al*, 1996).

Pathological classification of lymphoproliferative disorders associated with AAE

Haematoxylin–eosin stained slides were reviewed. Immunohistochemical staining using CD3, CD20, CD5, CD 10, CD23, BCL6 and cyclin D1 was performed on the diagnostic tissue biopsy in all patients with a diagnosis of lymphoproliferative disease. Lymphoproliferative disorders were classified according to the WHO classification (Swerdlow *et al*, 2008).

Results

Twenty-four of 72 AAE patients (33%) had an underlying B-cell NHL. Fifteen of 24 (62.5%) were diagnosed at onset of AAE or thereafter (3 months to 7 years). The remaining nine were diagnosed before the onset of AAE symptoms. According to the WHO classification (Swerdlow *et al*, 2008), 21 were indolent NHL and three aggressive NHL (two diffuse large B-cell lymphomas and one mantle cell lymphoma). Indolent NHLs were splenic MZL (SMZL, $n = 15$), LPL ($n = 3$), SLL ($n = 2$), follicular lymphoma ($n = 1$) (Fig 1). Serological evidence of HCV infection was detected only in 1 AAE patient with NHL. The clinical characteristics of AAE patients with indolent non-follicular NHL are reported in Table I.

Autoantibodies to C1-INH were detected in 13 of 24 (54%) NHL patients, including 12/15 (80%) cases with a diagnosis of SMZL.

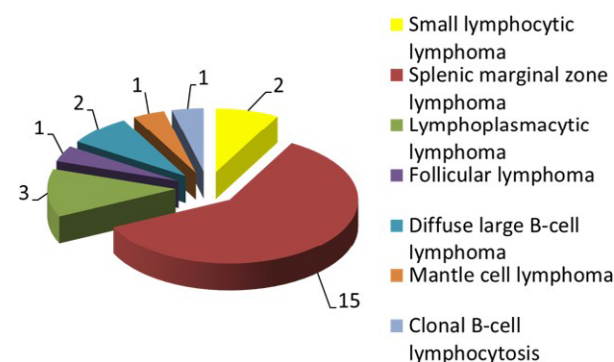


Fig 1. Lymphoproliferative diseases according to the World Health Organization classification in 24 out of 72 acquired angioedema patients.

Table I. Clinical Features of 20 AAE patients with indolent non follicular B-cell lymphoma

Median age (range)	64 (45–80)
Gender (male/female)	6/14
Performance Status (ECOG)	
0–1	20 (100%)
2–4	0
Ann Arbor Stage	
I/II	5 (25%)
III–IV	15 (75%)
B symptoms	
Absent	18 (90%)
Present	2 (10%)
Serum LDH levels	
Normal	15 (75%)
Elevated	5 (25%)
Unknown	0
Hemoglobin	
≥12 g/dl	8 (40%)
≤12 g/dl	12 (60%)
HCV antibody serological test	
Negative	19 (95%)
Positive	1 (5%)
Bone marrow involvement	
Absent	2 (10%)
Present	17 (85%)
Unknown	1 (5%)
International prognostic index (IPI)	
Low/low Intermediate	11 (55%)
High/high intermediate	9 (45%)
Treatment	
Chemotherapy	13 (65%)
Rituximab alone	2 (10%)
Radiotherapy	0 (0%)
Watchful wait	2 (10%)
Excision only	3 (15%)

ECOG, Eastern Cooperative Oncology Group; HCV, hepatitis C virus; LDH, lactic dehydrogenase.

Treatment outcome

Thirteen of the 20 patients with INFBCLs received systemic therapy alone. Chemotherapy regimens included: non-anthracycline-containing single agent regimen [chlorambucil or cyclophosphamide, vincristine and prednisone (CVP)] and anthracycline-containing regimen [cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)]. Five patients were treated with bendamustine and rituximab and achieved complete remission. Two patients received rituximab alone.

All three patients with high-grade malignancies were treated with anthracycline-containing regimens (CHOP and Rituximab) and all three died of lymphoproliferative disease progression.

Three patients were treated with splenectomy alone, achieving complete remission at 5, 6 and 2 years of follow-up, respectively. Two patients are still in watchful wait due

to stable disease. One patient with SMZL and concomitant HCV infection is currently receiving interferon α and ribavirin for viral eradication in preparation of possible chemotherapy. AAE patients did not seem to experience a significantly different rate of response to treatment as compared to patients with lymphoproliferative disease alone.

All patients treated with chemotherapy achieved, during therapeutic regimen or during remission, long lasting reduction of angioedema symptoms. For 12 of 18 patients, pre- and post-treatment complement parameters were available. All but one showed post-treatment improvement of complement abnormalities (Table II).

Discussion

Pathological B-cell proliferation, frequently with clonal characteristics, can lead to acquired C1-INH deficiency and production of neutralizing autoantibodies. The bridge between pathological B-cell clones and C1-INH deficiency is evidenced by the presence of monoclonal autoantibodies that cleave/inactivate C1-INH. When only MGUS or NHL are present, a cause-effect relationship is supported by: (i) extraordinarily higher prevalence of MGUS and NHL in AAE patients compared to the general population; (ii) some experimental evidence suggesting that lymphatic tissues from AAE patients fix C1-INH and/or activate the classical complement pathway; (iii) evidence that the M component in AAE recognizes C1-INH; (iv) scattered reports showing various degrees of reversal of the biochemical and/or clinical abnormalities of AAE upon therapeutically induced remission of NHL. This report described 24 AAE patients with associated lymphoproliferative disease, 20 of whom had INFBCLs. Several lymphoproliferative disorders appear to develop from transformation of a polyclonal proliferation of lymphocytes responding to antigenic and/or immunological drivers into a monoclonal/neoplastic population. This model has emerged with the description of several lymphomas developing in the context of chronic antigen-dependent immune stimulation, as reported for some infectious agents (e.g. *H pylori*-associated gastric mucosa-associated lymphoid tissue lymphoma, HCV-associated lymphoproliferative diseases) or autoimmune drivers (e.g. Sjögren-associated lymphoproliferative diseases). In this study, we found that AAE is associated with an increased risk of NHL compared to general population. Interestingly, this study also suggests that the risk of lymphoproliferative disease is confined to specific histotypes that are rare in the general population (Armitage & Weisenburger, 1998). Our finding is supported by additional scattered reports showing high prevalence of INFBCL, especially MZL and SMZL in patients with AAE (Sugisaki *et al*, 2007; Lam *et al*, 2012; Ates *et al*, 2015).

Our series is the largest reported to date and confirms that SMZL represents the most common histotype among AAE patients, with a frequency of 75% of INFBCL (15/20 indolent lymphoproliferative disease) and of 62.5% of all lymphopro-

Table II. Effect of treatment of the lymphoproliferative disease on clinical and biochemical parameters of angioedema due to acquired C1 inhibitor deficiency.

Patient	Diagnosis	Treatment regimen	*Clinical improvement of angioedema after treatment	†Complement parameters at diagnosis	‡Complement parameters after treatment
1	LPL	R-CHOP	Complete	C1-INH f: <10 C1-INH Ag: 31 C4: <10 C1q: 97	C1-INH f: 116 C1-INH Ag: 115 C4: 146 C1q: 86
2	LPL	Rituximab + Fludarabine	Complete	C1-INH f: <10 C1-INH Ag: <10 C4: <10 C1q: <10	C1-INH f: 30 C1-INH Ag: 50 C4: <10 C1q: 100
3	SLL	Chorambucil	Complete	C1-INH f: <10 C1-INH Ag: <10 C4: <10 C1q: <10	NA
4	SLL	Bendamustine+ Rituximab	Complete	C1-INH f: <10 C1-INH Ag: 9 C4: <10 C1q: 25	C1-INH f: 30 C1-INH Ag: 50 C4: <10 C1q: 100
5	SMZL	R-CHOP	Complete	C1-INH f: <10 C1-INH Ag: <10 C4: <10	C1-INH f: 82 C1-INH Ag: 100 C4: 25
6	SMZL	Splenectomy	Complete	C1-INH f: <10 C1-INH Ag: <10 C4: <10	C1-INH f: 52 C1-INH Ag: NA C4: <10
7	SMZL	CTX Prednisone	Complete	C1-INH f: 31 C1-INH Ag: 50 C4: <10	NA
8	SMZL	R-CVP	Complete	C1-INH f: <10 C1-INH Ag: <10 C4: <10	C1-INH f: 30 C1-INH Ag: 50 C4: <10
9	SMZL	R-CVP	Complete	C1-INH f: 22 C1-INH Ag: <10 C4: <10	C1-INH f: 82 C1-INH Ag: 90 C4: 60
10	SMZL	Splenectomy	Complete	C1-INH f: 18 C1-INH Ag: <10 C4: 25	C1-INH f: 32 C1-INH Ag: 25 C4: 25
11	SMZL	Splenectomy	Partial	C1-INH f: 18 C1-INH Ag: <10 C4: 25	NA
12	SMZL	CTX Prednisone	Partial	C1-INH f: <10 C1-INH Ag: <10 C4: 25	NA
13	SMZL	Rituximab+ Bendamustine	Complete	C1-INH f: <10 C1-INH Ag: <10 C4: <10	NA
14	SMZL	Rituximab+ Bendamustine	Complete	C1-INH f: 37 C1-INH Ag: <25 C4: <10	C1-INH f: 73 C1-INH Ag: 70 C4: 25
15	SMZL	Rituximab+ Bendamustine	Complete	C1-INH f: <10 C1-INH Ag: <10 C4: <10	NA
16	SMZL	Rituximab+ Bendamustine	Complete	C1-INH f: 33 C1-INH Ag: <10 C4: 25	C1-INH f: 73 C1-INH Ag: 70 C4: 25

Table II. (Continued)

Patient	Diagnosis	Treatment regimen	*Clinical improvement of angioedema after treatment	†Complement parameters at diagnosis	†Complement parameters after treatment
17	SMZL	Rituximab alone	Complete	C1-INH f: 40 C1-INH Ag: 48 C4: 25	C1-INH f: 71 C1-INH Ag: 100 C4: 50
18	LPL	Rituximab alone	Complete	C1-INH f: 30 C1-INH Ag: 25 C4: 25	C1-INH f: 100 C1-INH Ag: 144 C4: 31

C1-INH f, inhibitor of complement component 1 function; C1-INH Ag, inhibitor of complement component 1 antigen; C4, complement component 4; C1q, complement component 1, q subcomponent; LPL, lymphoplasmocytic lymphoma; SLL, small lymphocytic lymphoma; SMZL, splenic marginal zone lymphoma; R – CHOP, rituximab–cyclophosphamide, doxorubicin, vincristine, prednisone; CEOP, (cyclophosphamide, Etoposide, Prednisolone, Vincristine; R CVP, rituximab, cyclophosphamide, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; CTX, Cyclophosphamide; NA, not available.

*Complete: <1 angioedema attack/year. Partial: 50% reduction in attacks frequency compared to pre-treatment.

†Parameters (see text) are expressed as percentage of normal pooled plasma.

liferative diseases identified. Histologically, the marginal zone surrounding the follicular areas is expanded and neoplastic cells have cytological and phenotypical features of marginal zone lymphocytes, clearly distinguishing them from the lymphocytes present in the follicular centre or mantle cell area (Troussard *et al*, 1996).

Despite being aware of the undeniable limits of histology, we speculate that the post-germinal origin of INFBCLs, especially MZL, might suggest an antigen-driven mechanism of lymphomagenesis in AAE patients. Some experimental studies pointed to NOTCH and NF- κ B signalling as a strong driver of autoimmunity and lymphoproliferation and further research is needed to investigate the role of the activation of these pathways for lymphomagenesis in our AAE population (Rossi *et al*, 2011, 2012).

Next-generation sequencing studies have identified somatic mutations of myeloid differentiation primary response 88 (MYD88), a key component of the Toll-like receptor signalling machinery, in ~90% of LPL and in MZLs. There is evidence to consider MYD88 L265P mutation as the first genetic hit that induces signalling cascades leading to NF- κ B and JAK-STAT3 activation [with further enhancement due to Bruton tyrosine kinase (BTK) activation]. Additional genetic and epigenetic hits follow over time, with final B-cell deregulation and tumour progression (Poulain *et al*, 2013; Yang *et al*, 2013).

MYD88 is mutated in a variety of mature B-cell tumours. Among indolent B-cell malignancies, MYD88 mutations tend to cluster with LPL/Waldenström macroglobulinaemia, where they occur in ~90% of cases (Spina *et al*, 2015). MYD88 mutations are also present in a significant fraction of IgM-secreting monoclonal gammopathies of undetermined significance (MGUS), where they are currently detected in ~60–80% of cases, thus pointing to MYD88 mutations as an early genetic event in the development of lymphoplasmacytic tumours. Rare MYD 88 mutations are also found in SMZL and CLL. Among aggressive B-cell malignancies, MYD88

mutations have been identified in ~30% of DLBCL (Fabbri *et al*, 2011; Rossi *et al*, 2012; Xu *et al*, 2014).

Despite the reported association between INFBCL (especially MZL and LPL) and HCV infection (Arcaini *et al*, 2012), in our case series only one patient had HCV infection.

Autoimmune manifestations, including immune-mediated pancytopenia, haemolytic anaemia, immune-mediated thrombocytopenia, skin blistering disease, immune-mediated neuropathies and autoantibodies to clotting factors may be included in the lymphoproliferative disorders (Castelli *et al*, 2002, 2012; Zhang *et al*, 2006; Ramchandren & Lisak, 2010; Seffo & Daw, 2010). MZL and SLL are particularly frequent in autoimmune manifestations, especially in MZL patients with a strict IGHV1-2 gene frequency (Chiorazzi *et al*, 2005; Hodgson *et al*, 2011; Brisou *et al*, 2014).

Autoantibodies to C1-INH were detectable in nine of 15 patients with SMZL, one of who had a concomitant autoimmune haemolytic anaemia. This finding suggests that auto reactivity to this protein is not part of a generic tendency to autoimmunity, but a specific feature of the disease. Further investigations are needed to detail the effect of this protein on lymphocyte proliferation.

In conclusion, our study suggests that B-cell proliferation, frequently with clonal characteristics, is associated with acquired C1-INH deficiency and can be responsible for the production of neutralizing autoantibodies as well as for increased risk of lymphoproliferative disease. The post-germinal centre origin of most of lymphomas observed in our population seems to suggest that a chronic immune stimulation may contribute to lymphomagenesis. C1-INH belongs to the protein family of serine protease inhibitors and undergoes major structural changes to interact with its target proteases (Silverman *et al*, 2001). Hence, we speculate that a still unknown event causes abnormal persistence of hidden epitopes not recognized as ‘self’ during inhibitor-protease

interaction and initiates the autoimmune response that cross-reacts with the native protein.

Author contributions

R Castelli, D. Rossi, M Wu and M. Cicardi designed the study, interpreted data and wrote the manuscript. M Arquati

and A Zanichelli performed diagnosis, provided well characterized pathological samples and contributed to study design and data interpretation. C Suffritti performed and interpreted complement parameters, performed bioinformatic analysis and contributed to study design and data interpretation.

References

- Alsenz, J., Bork, K. & Loos, M. (1987) Autoantibody-mediated acquired deficiency of C1 inhibitor. *New England Journal of Medicine*, **316**, 1360–1366.
- Arcaini, L., Merli, M., Volpetti, S., Rattotti, S., Gotti, M. & Zaia, F. (2012) Indolent B cell lymphomas associated with HCV infection: clinical and virological features and role of antiviral therapy. *Clinical and Developmental Immunology*, **2012**, 638185.
- Armitage, J.O. & Weisenburger, D.D. (1998) New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *Journal of Clinical Oncology*, **16**, 2780–2795.
- Ates, O., Sunar, V., Babacan, T., Akin, S., Kertmen, N. & Altundag, K. (2015) Acquired C1 esterase inhibitor deficiency in a marginal zone lymphoma patient treated with rituximab. *Journal of BUON*, **20**, 349.
- Branellec, A., Bouillet, L., Javaud, N., Mekinian, A., Boccon-Gibod, I., Blanchard-Delaunay, C., Oksenhendler, E., Ollivier, Y., Dunogue, B., Amarger, S., Ponard, D., Drouet, C., Mouthon, L., Thomas, M., Fain, O. & French National Reference Center for, A. (2012) Acquired C1-inhibitor deficiency: 7 patients treated with rituximab. *Journal of Clinical Immunology*, **32**, 936–941.
- Brisou, G., Verney, A., Wenner, T., Baseggio, L., Felman, P., Callet-Bauchu, E., Coiffier, B., Berger, F., Salles, G. & Traverse-Glehen, A. (2014) A restricted IGHV gene repertoire in splenic marginal zone lymphoma is associated with autoimmune disorders. *Haematologica*, **99**, e197–e198.
- Castelli, R., Vismara, A., Pavia, G., Dagani, R. & Porro, T. (2002) Relapsing pure red cell aplasia associated with B-cell chronic lymphocytic leukemia successfully treated by intravenous immunoglobulin concentrate. *Annali Italiani di Medicina Interna*, **17**, 47–50.
- Castelli, R., Deliliers, D.L., Zingale, L.C., Pogliani, E.M. & Cicardi, M. (2007) Lymphoproliferative disease and acquired C1 inhibitor deficiency. *Haematologica*, **92**, 716–718.
- Castelli, R., Gritti, G., Cannavo, A., Moreo, G., Conti, G., Reda, G. & Cortelezzi, A. (2012) Successful management with intravenous immunoglobulins in alemtuzumab-induced acute inflammatory demyelinating neuropathy: clinical report of three patients. *Immunopharmacology and Immunotoxicology*, **34**, 717–720.
- Chiorazzi, N., Rai, K.R. & Ferrarini, M. (2005) Chronic lymphocytic leukemia. *New England Journal of Medicine*, **352**, 804–815.
- Cicardi, M., Beretta, A., Colombo, M., Gioffre, D., Cugno, M. & Agostoni, A. (1996) Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angioedema. *Clinical and Experimental Immunology*, **106**, 475–480.
- Cicardi, M., Zingale, L.C., Pappalardo, E., Folcioni, A. & Agostoni, A. (2003) Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. *Medicine (Baltimore)*, **82**, 274–281.
- Cugno, M., Zanichelli, A., Foiemi, F., Caccia, S. & Cicardi, M. (2009) C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. *Trends in Molecular Medicine*, **15**, 69–78.
- Fabbri, G., Rasi, S., Rossi, D., Trifonov, V., Khianian, H., Ma, J., Grunn, A., Fangazio, M., Capello, D., Monti, S., Cresta, S., Gargiulo, E., Forconi, F., Guarini, A., Arcaini, L., Paulli, M., Laurenti, L., Larocca, L.M., Marasca, R., Gattei, V., Oscier, D., Bertoni, F., Mullighan, C.G., Foa, R., Pasqualucci, L., Rabadan, R., Dalla-Favera, R. & Gaidano, G. (2011) Analysis of the chronic lymphocytic leukemia coding genome: role of NOTCH1 mutational activation. *Journal of Experimental Medicine*, **208**, 1389–1401.
- Franklin, J., Lunt, M., Bunn, D., Symmons, D. & Silman, A. (2006) Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis. *Annals of the Rheumatic Diseases*, **65**, 617–622.
- Hodgson, K., Ferrer, G., Montserrat, E. & Moreno, C. (2011) Chronic lymphocytic leukemia and autoimmunity: a systematic review. *Haematologica*, **96**, 752–761.
- Lam, D.H., Levy, N.B., Nickerson, J.M., Gruenberg, D.A. & Lansigan, F. (2012) Acquired angioedema and marginal zone lymphoma. *Journal of Clinical Oncology*, **30**, e151–e153.
- Poulain, S., Roumier, C., Decambon, A., Renneville, A., Herbaux, C., Bertrand, E., Tricot, S., Daudignon, A., Galiegue-Zouitina, S., Soenen, V., Theisen, O., Grardel, N., Nibourel, O., Roche-Lestienne, C., Quesnel, B., Duthilleul, P., Preudhomme, C. & Leleu, X. (2013) MYD88 L265P mutation in Waldenstrom macroglobulinemia. *Blood*, **121**, 4504–4511.
- Ramchandren, S. & Lisak, R.P. (2010) The immunopathogenesis of Guillain-Barre syndrome. *Clinical Advances in Hematology and Oncology*, **8**, 203–206.
- Rossi, D., Deaglio, S., Dominguez-Sola, D., Rasi, S., Vaisitti, T., Agostinelli, C., Spina, V., Brusca, A., Monti, S., Cerri, M., Cresta, S., Fangazio, M., Arcaini, L., Lucioni, M., Marasca, R., Thieblemont, C., Capello, D., Facchetti, F., Kwee, I., Pileri, S.A., Foa, R., Bertoni, F., Dalla-Favera, R., Pasqualucci, L. & Gaidano, G. (2011) Alteration of BIRC3 and multiple other NF-kappaB pathway genes in splenic marginal zone lymphoma. *Blood*, **118**, 4930–4934.
- Rossi, D., Trifonov, V., Fangazio, M., Brusca, A., Rasi, S., Spina, V., Monti, S., Vaisitti, T., Arruga, F., Fama, R., Ciardullo, C., Greco, M., Cresta, S., Piranda, D., Holmes, A., Fabbri, G., Messina, M., Rinaldi, A., Wang, J., Agostinelli, C., Piccaluga, P.P., Lucioni, M., Tabbo, F., Serra, R., Franceschetti, S., Deambrogi, C., Daniele, G., Gattei, V., Marasca, R., Facchetti, F., Arcaini, L., Inghirami, G., Bertoni, F., Pileri, S.A., Deaglio, S., Foa, R., Dalla-Favera, R., Pasqualucci, L., Rabadan, R. & Gaidano, G. (2012) The coding genome of splenic marginal zone lymphoma: activation of NOTCH2 and other pathways regulating marginal zone development. *Journal of Experimental Medicine*, **209**, 1537–1551.
- Seffo, F. & Daw, H.A. (2010) Non-Hodgkin lymphoma and Guillain-Barre syndrome: a rare association. *Clinical Advances in Hematology and Oncology*, **8**, 201–203.
- Silverman, G.A., Bird, P.I., Carrell, R.W., Church, F.C., Coughlin, P.B., Gettins, P.G., Irving, J.A., Lomas, D.A., Luke, C.J., Moyer, R.W., Pemberton, P.A., Remold-O'Donnell, E., Salvesen, G.S., Travis, J. & Whisstock, J.C. (2001) The serpins are an expanding superfamily of structurally similar but functionally diverse proteins. Evolution, mechanism of inhibition, novel functions, and a revised nomenclature. *Journal of Biological Chemistry*, **276**, 33293–33296.
- Spina, V., Martuscelli, L. & Rossi, D. (2015) Molecular deregulation of signaling in lymphoid tumors. *European Journal of Haematology*, **95**, 257–269.
- Sugisaki, K., Itoh, K. & Tamaru, J. (2007) Acquired C1-esterase inhibitor deficiency and positive lupus anticoagulant accompanied by splenic marginal zone B-cell lymphoma. *Clinical and Experimental Rheumatology*, **25**, 627–629.
- Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J. & Vardiman, J.W. (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tis-

- sues, 4th edn. International Agency for Research on Cancer Press, Lyon, France.
- Troussard, X., Valensi, F., Duchayne, E., Garand, R., Felman, P., Tulliez, M., Henry-Amar, M., Bryon, P.A. & Flandrin, G. (1996) Splenic lymphoma with villous lymphocytes: clinical presentation, biology and prognostic factors in a series of 100 patients. Groupe Francais d'Hematologie Cellulaire (GFHC). *British Journal of Haematology*, **93**, 731–736.
- Wotherspoon, A.C., Ortiz-Hidalgo, C., Falzon, M.R. & Isaacson, P.G. (1991) *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. *Lancet*, **338**, 1175–1176.
- Xu, L., Hunter, Z.R., Yang, G., Cao, Y., Liu, X., Manning, R., Tripsas, C., Chen, J., Patterson, C.J., Kluk, M., Kanan, S., Castillo, J., Lindeman, N. & Treon, S.P. (2014) Detection of MYD88 L265P in peripheral blood of patients with Waldenstrom's Macroglobulinemia and IgM monoclonal gammopathy of undetermined significance. *Leukemia*, **28**, 1698–1704.
- Yang, G., Zhou, Y., Liu, X., Xu, L., Cao, Y., Manning, R.J., Patterson, C.J., Buhrlage, S.J., Gray, N., Tai, Y.T., Anderson, K.C., Hunter, Z.R. & Treon, S.P. (2013) A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia. *Blood*, **122**, 1222–1232.
- Zhang, B., Zheng, R., Wang, J., Bu, D. & Zhu, X. (2006) Epitopes in the linker subdomain region of envoplakin recognized by autoantibodies in paraneoplastic pemphigus patients. *Journal of Investigate Dermatology*, **126**, 832–840.
- Zingale, L.C., Castelli, R., Zanichelli, A. & Cicardi, M. (2006) Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunology and Allergy Clinics of North America*, **26**, 669–690.