

EXPERT REVIEWS

Development of autoimmunity in lymphoma

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Development of lymphoproliferative diseases during the course of autoimmune and chronic inflammatory conditions is well established. Conversely, development of clinical or biological signs of autoimmunity at the time of the diagnosis of lymphoma or during its course indicates that lymphoma and autoimmune manifestations may constitute two faces of the same process. The aim of this review is to describe autoimmune manifestations related to non-Hodgkin's lymphoma and Hodgkin's lymphoma, their specificity according to the lymphoma subtype and their physiopathological signification. Lymphoma-related autoimmune manifestations include mainly skin diseases, hematological manifestations, rheumatic diseases and renal lesions. Despite the lack of studies providing a systematic prospective assessment, autoimmune manifestations are observed in all lymphoma subtypes and seem particularly prevalent in marginal-zone lymphoma and T-cell lymphoma. Autoimmune manifestation's physiopathology may implicate production of autoantibodies by CD5-positive autoreactive B cells, a loss of immune tolerance, an alteration of the Fas/Fas-ligand pathway and/or a chronic antigenic stimulation. Monoclonal antibodies (including rituximab, Campath-1H or epratuzumab) constitute the most promising approach to treat lymphoma-related immune disorders.

KEYWORDS: antinuclear antibody • autoimmunity • Hodgkin's lymphoma • marginal-zone lymphoma • mixed cryoglobulinemia • non-Hodgkin's lymphoma • rituximab

Development of lymphoproliferative diseases, particularly non-Hodgkin's lymphoma (NHL), during the course of certain autoimmune and chronic inflammatory conditions is well established. Meta-analysis and prospective cohort studies have demonstrated that there is an increased risk of NHL in patients with rheumatoid arthritis (RA), primary Sjögren syndrome (pSS) or systemic lupus erythematosus (SLE) [1]. Similarly, development of clinical or biological signs of autoimmunity at the time of the initial diagnosis of lymphoma or during its course represents the other end of the spectrum of the inter-relationships linking lymphoproliferative malignancies and autoimmune diseases. This review will describe clinical and biological autoimmune manifestations observed in NHL or Hodgkin's lymphoma (HL), their characteristics according to the lymphoma subtype and discuss the hypothetical mechanisms that lead to disordered immunoregulation.

Spectrum of autoimmune clinical manifestations in lymphoma

For a summary of the autoimmune clinical manifestations in lymphomas see TABLE 1.

Cutaneous manifestations

Paraneoplastic pemphigus

NHL represents the most frequently associated cancer, followed by chronic lymphocytic leukemia (CLL), Castleman's disease, thymoma, sarcoma and Waldenström's macroglobulinemia (WM) [2–4]. In 70% of cases, lymphoma and pemphigus manifestations occur simultaneously. In some cases, the autoimmune skin disease can precede the diagnosis of lymphoma by a few months. Clinical signs are polymorphous, including cutaneomucosal manifestations of pemphigus vulgar (skin and mucosa erosion, fragile intradermal bullae with Nikolski's sign), pemphigoid (urticaria, distended subepidermal bullae) and polymorphous erythema (plaque lesions). Mucosal erosions predominate and buccal or lips involvement are frequently observed. Conjunctives and perineal area are also frequently altered. Intrabronchial and esophageal lesions are rarely observed and can be life-threatening, participating to a paraneoplastic autoimmune multiorgan syndrome [5].

Pathological criteria have been proposed, including keratinocyte necrosis, suprabasal keratinocyte vacuolization and intraepidermal

Table 1. Autoimmune manifestations in lymphomas.

Clinical and biological autoimmune manifestations	Frequency of autoimmune manifestation in lymphoma		Frequency of lymphoma associated with autoimmune manifestation (%)	Remarks	Ref.
	NHL (all) (%)	NHL subtype (%)	HL (%)		
Cutaneous manifestations					
Urticaria, rash	-	ALL-T: 46	-	Highly prevalent in ALL-T	[149]
Vasculitis	9.5	CLL: 6	-	Including cutaneous leukocytoclastic angitis and cutaneous lymphocytic vasculopathy	[8]
Raynaud's phenomenon, livedo reticularis, acrocyanosis	-	-	-	Usually related to cold agglutinins or rarely to cryofibrinogen	[14,15]
Angioedema	-	-	-	Secondary to antibody directed against C1 inhibitor	[18]
Paraneoplastic pemphigus	-	-	-	Buccal or lips involvement are frequently observed	[3]
Dermatitis herpetiformis	-	-	-	Associated with other systemic autoimmune disorders and antiendomysium antibodies	[22]
Neurological manifestations					
Demyelinating neuropathy	-	-	-	Autoantibodies reacting with the myelin-associated glycoprotein, sulfatide, GD1b ganglioside or GM1 ganglioside	[23–25]
Guillain-Barre syndrome and subacute polyradiculoneuropathy	-	-	-	Mainly reported in HL and observed following ASCT and during rituximab maintenance therapy	[28]
Paraneoplastic subacute sensory neuropathy (Denny-Brown syndrome)	-	-	-	Exceptional in lymphoma, reported in HL, related to the presence of anti-Hu antibodies	[27,31]
Autoimmune retinopathy	-	-	-	Reported in HL	[40]
Cerebellar degeneration	-	-	-	Reported in HL with antibodies directed against components of Purkinje cells	[31]
Granulomatous angiitis	-	-	-	Mainly reported in HL	[36]
Bilateral granulomatous panuveitis (Vogt–Koyanagi–Harada disease)	-	-	-	Differential diagnosis include primary intraocular B-cell lymphoma	[38]
Myasthenia gravis	-	-	-	Acetylcholine receptor autoantibody is used as a tumor marker	[34]
Lambert–Eaton syndrome	-	-	-	Reported in NHL and HL	[33]
Autoimmune manifestation frequencies are indicated when data from prospective or retrospective cohorts are available in the literature. In most cases, the exact prevalence of the autoimmune manifestations is undetermined (-). AIHA: Autoimmune hemolytic anemia; ALL-T: Angioimmunoblastic T-cell lymphoma; ASCT: Autologous stem cell transplantation; CLL: Chronic lymphocytic leukemia; HL: Hodgkin's lymphoma; MZL: Marginal-zone lymphoma; NHL: Non-Hodgkin's lymphoma; RS3PE: Remitting seronegative symmetrical synovitis with pitting edema; WM: Waldenström macroglobulinemia.					

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	NHL (all) (%)	NHL subtype (%)			
Hematological manifestations					
Hemolytic anemia	3–18	CLL: 2–10; AIL-T: 40–78	0.2	16 (WM)	[41–45,135, 148,149]
Cold-agglutinin disease	1.1–4.9	14		76 (NHL)	[47]
Thrombocytopenia and Evans syndrome	5% after ASCT	-	1	-	[43,118]
Neutropenia	24.9 following rituximab therapy			-	[61,128]
Erythroblastopenia	-	-	-	-	[44,51]
Acquired hemostatic abnormalities	-	-	-	10 (NHL), 14 (CLL)	[64]
Antiphospholipid antibodies	26.6–41	-	-	-	[96,97]
Rheumatic manifestations					
Seronegative arthritis, RS3PE, sacroiliitis	-	-	-	-	[71]
Adult-onset Still disease	-	-	-	-	[73]
Eosinophilic fasciitis	-	-	-	40	[75]
Systemic sclerosis	-	-	-	-	[76]
Polymyositis and dermatopolymyositis	-	-	-	3 (NHL), 6 (HL)	[78]
Medium and large-vessel vasculitis, including giant-cell (temporal) arteritis and polyarteritis nodosa	-	-	-	-	[6]
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Renal manifestations					
Type I and type II mixed cryoglobulinemia	-	-	3–38; 29 (WM)	Mainly associated with HCV infection (type II)	[79,80]
Glomerulonephritis	5	-	-	Membranoproliferative glomerulonephritis is the most frequent glomerular lesion	[82]
Henoch–Schönlein purpura	-	-	-	Observed in NHL and HL	[85]
Endocrinopathies and gastroenterological manifestations					
Thyroiditis	3 after ASCT	-	-	Mainly observed secondary to cervical radiotherapy in HL	[112–114]
Anti-transglutaminase and antiendomysial antibodies	10	-	-	Highly prevalent without any clinical manifestations	[103]
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acantholysis, but are unspecific. Immunohistological findings reveal antibody and complement deposits at the dermo-epidermal junction and within the keratinocytes by staining for human IgG and C3. The diagnosis is based on the identification of autoantibodies and their target antigens by immunoprecipitation or immunoblotting. Antibodies are directed against plakin components (desmoplakin I and II, peripakin and envopakin), the major pemphigoid antigen (desmoglein 1 and 3) and certain yet unidentified antigens with a molecular weight of 170 kDa [3].

Vasculitis

Cutaneous leukocytoclastic angiitis is a small vessel vasculitis confined to the skin involving dermal post-capillary venules. This is the most frequent vasculitis occurring in a close temporal relationship with lymphoma and can be observed independently of drug exposure, infectious diseases or cryoglobulinemia [6,7].

Cutaneous lymphocytic vasculopathy is a common paraneoplastic skin manifestation in patients with lymphoproliferative diseases, especially in CLL and T-cell NHL. It is characterized by lymphocytic vasculitis with perivascular infiltration by nonmalignant T lymphocytes. A maculopapular rash, commonly found in the upper and lower extremities (FIGURE 1), clinically characterizes this vasculitis. Pruritus of varying intensity is usual [8].

In most cases vasculitis is limited to the skin but systemic antineutrophil cytoplasmic antibody (ANCA) vasculitis, complicated by a pulmonary–renal syndrome with alveolar hemorrhage, has also been described [9].

Cryoglobulinemic vasculitis can be suspected in case of infiltrated purpura, urticaria or leg ulcers [10]. The most frequent associated manifestations are arthralgia and nephritis. Type I and type II mixed cryoglobulinemia with rheumatoid factor are typically detectable in serum.

Medium and large-vessel vasculitis, including giant-cell (temporal) arteritis and polyarteritis nodosa have been reported anecdotally in a temporal relationship with lymphoma [6,11–13].

Other cutaneous manifestations

Livedo reticularis, Raynaud's phenomenon or acrocyanosis can reveal the presence of cold agglutinins or less frequently be the consequence of a cryofibrinogen related to lymphoproliferative diseases [14–16]. Angioedema due to acquired deficiency of the C1 inhibitor are commonly related to various forms of B-cell disorders, including monoclonal gammopathies of unknown significance (MGUS) and NHL [17,18].

Neutrophilic dermatosis (Sweet's syndrome, pyoderma gangrenosum and erythema elevatum diutinum) are mainly observed in the setting of myeloid diseases and are rarely



Figure 1. Cutaneous lymphocytic vasculopathy in a 58-year-old woman with follicular lymphoma.

associated to lymphomas [19–21]. Retrospective analysis of a large series of 264 dermatitis herpetiformis has shown that this cutaneous manifestation of gluten sensitivity can be associated with a low frequency (3%) to NHL [22].

Neurologic manifestations

Monoclonal gammopathies, including MGUS and WM, are frequently associated with neuropathy. IgM antibodies reacting with the myelin-associated glycoprotein play a pathogenic role and are associated with a chronic, slowly progressive, predominantly sensory demyelinating neuropathy [23]. Similarly, lymphoma cells can produce monoclonal antibodies directed against others glycolipids, such as GM1 and GD1b, and lead to a multifocal motor neuropathy. Pathological nerve examination demonstrates severe widespread demyelination without lymphoma cell infiltration in the peripheral nerves [24,25].

The Denny–Brown syndrome is a subacute sensory neuropathy characterized by a severe inflammatory loss of the dorsal root ganglia. Clinically a severe asymmetric sensory neuropathy progressing over a few weeks is observed. The underlying cancer is most exclusively a small-cell lung cancer and related to the presence of anti-Hu antibodies [26]. In a series of 162 patients with anti-Hu antibodies, only one NHL case was noticed among the ten non-small-cell lung cancers [27]. In addition, sensitive neuropathy may be observed with a mixed cryoglobulinemia related to lymphoproliferative disorders [23].

Guillain–Barré syndrome (GBS) corresponding to an inflammatory demyelinating symmetrical polyneuropathy involving peripheral and cranial nerves and roots has been described in association with HL and can be observed exceptionally in NHL, and in some cases following autologous bone marrow transplantation [28,29]. More frequently, subacute polyneuropathy can reveal the lymphoma, without any evidence for a nervous system infiltration [30].

Paraneoplastic syndromes involving the CNS are exceptionally related to lymphoma. Anecdotal cerebellar degeneration related to the production of antibodies directed against components of Purkinje cells (anti-Tr and anti-mGLuR1) in HL [31] or ataxia with opsoclonus–myoclonus without any evidence of neural antibodies related to T-cell NHL has been described [32]. Lambert–Eaton myasthenic syndrome, a presynaptic neuromuscular junction disorder typically associated with small-cell lung carcinoma can be associated rarely with lymphoproliferative disorders [33]. Elevation of acetylcholine receptor antibody titer, a hallmark of myasthenia gravis, was an unusual marker in a lymphoblastic lymphoma case that normalized following chemotherapy. Thymic infiltration by lymphoma cells may be involved in the pathogenesis of myasthenia gravis-related lymphoma [34,35].

Granulomatous angiitis of the CNS is a rare cause of neurological deterioration that can be associated with HL in 5–22% of cases [36]. Clinical manifestations are various as a consequence of a multifocal involvement and include confusion, headache, crisis and focal deficiency. Magnetic resonance imaging reveals multifocal ischemic lesions. Stereotaxic biopsy, when possible, confirms the diagnosis and reveals granulomatous angiitis involving both intracerebral and small leptomeningeal vessels [36]. Differential diagnosis includes lymphomas with intravascular development [37]. In addition, Vogt–Koyanagi–Harada disease, an inflammatory ocular disorder characterized by bilateral granulomatous panuveitis, related to an aberrant T-cell-mediated immune response directed against self-antigens found on melanocytes, has been reported in a few cases in association with NHL [38,39]. Paraneoplastic retinopathy has been mainly recognized in solid tumors, including melanoma and gynecologic carcinoma [40]. Lymphoma-associated retinopathy has been also reported in association with HL. Pathogenesis of the retinal degeneration may be related to an antibody reacting to an unknown retinal protein of 65 kDa [40].

Hematological manifestations

Hemolytic anemia & pure red cell aplasia

In a retrospective study of 83 acquired autoimmune hemolytic anemia (AIHA) cases, Genty *et al.* reported an association with NHL in 17% of cases. This frequency was similar to AIHA related to connective tissue disease [41]. In almost half of cases, the onset of AIHA precedes the NHL (from 22 to 66 months). Predictive factors related to the occurrence of lymphoma in this setting are the presence of a monoclonal component, hypogammaglobulinemia and other autoimmune manifestations [41,42]. However, except in lymphocytic lymphoma and angioimmunoblastic T-cell lymphoma (AIL-T), AIHA is relatively uncommon in lymphoma, occurring in less than 5% of cases in large series of HL and NHL [43,44]. It is of note that some histological NHL subtypes, such as T-cell lymphoma and marginal-zone lymphoma (MZL), are more frequently associated with AIHA [45].

In 80% of cases, AIHA is related to warm-reactive antibodies and more rarely to an IgM cold-reactive antibody [45]. ‘Idiopathic’ cold-agglutinin disease (CAD) can be diagnosed before the occurrence of a true lymphoma and is almost constantly related to detectable symptom-producing monoclonal lymphoproliferative disorder at the time of diagnosis [46,47]. In a series of 86 patients with CAD, an underlying lymphoma was observed in 76% of cases, including a lymphoplasmocytic lymphoma subtype in 50% of cases [48].

Exceptionally, paroxysmal cold hemoglobinuria secondary to a biphasic polyclonal IgG autoantibody (Donath–Landsteiner antibody) can reveal a NHL [49]. Warm autoantibody responsible for peripheral red blood cell destruction can also suppress bone marrow erythropoiesis, leading to a pure red cell aplasia [44,50,51].

Autoimmune thrombocytopenia

Immune-mediated thrombocytopenia is a well-known complication of lymphoproliferative diseases, despite it being relatively uncommon in NHL, occurring in 0.2% of cases in a large series of 515 NHL patients and in 5% of HL [43,52]. Autoimmune thrombocytopenia can be the sole manifestation of the lymphoma of any histological subtype with nodal or extranodal involvement [53,54]. Thrombocytopenia can appear several years before the emergence of lymphoma, in our experience justifying the performance of CT-scan imaging on patients older than 60 years of age in cases of autoimmune thrombocytopenia. It has been demonstrated that lymphoma cells themselves produce antibodies directed against platelet glycoproteins Ib or IIb/IIIa [55–57]. In addition, autoantibodies can induce qualitative platelet function impairment by blocking IIb/IIIa glycoprotein (acquired Glanzmann’s thrombasthenia) [55,58].

Autoimmune neutropenia

Primary autoimmune neutropenia (AIN) is usually observed in children. Secondary AIN is relatively common during the course of connectivites, including RA (Felty’s syndrome), pSS or SLE. It is of note that neutropenia in the setting of lymphoproliferative disease evokes the diagnosis of lymphoproliferative disorders of granular lymphocytes (LDGL), which include large granular lymphocyte (LGL) leukemia, Felty’s syndrome, T- γ lymphocytosis and T- or natural killer–LGL leukemia [59].

By contrast, the relationship between AIN and lymphoma is less documented and such association seems very rare. Diagnosis of AIN is based on the demonstration of the presence of autoantibodies directed against neutrophil-specific antigens, such as CD16 [60]. In some cases, lymphoma B cells can generate monoclonal antibodies against the ‘i’ antigen and be responsible for both AHAI and AIN [61].

AIN related to gastric mucosae-associated lymphoma tissues (MALT) lymphoma and recovery of the neutrophil count after *Helicobacter pylori* eradication therapy has been reported, suggesting an inter-relationship between lymphoma, chronic infectious disease and autoimmunity [62].

Specific aspects of late neutropenia following rituximab treatment are addressed below.

Acquired hemostatic abnormalities

The hemostatic system is often activated in cancer patients that results in an increase of thrombotic events. By contrast, bleeding manifestations related to acquired hemostatic abnormalities secondary to autoantibodies with hemostatic inhibitor activity have been reported, especially in lymphoma. Treatment of cancer with chemotherapy or surgery may accelerate the eradication of the inhibitor in some patients.

Hemostatic inhibitor antibodies directed against factor VIII or the von Willebrand factor VIII complex are the most commonly reported in cancer. Acquired prothrombin deficiency secondary to antibody interacting with a calcium-dependent epitope has been also described in low-grade lymphoma [63]. Overall, hematological malignancies, including lymphoma, CLL, acute leukemia and myelodysplastic syndromes, are responsible for approximately 40% of acquired hemophilia [64].

Rheumatic manifestations

The spectrum of rheumatic manifestations described in lymphoma is wide and raises the question of a fortuitous association rather than a true causal relationship [65–67]. Bilateral knee effusions, sacroiliitis and monoarthritis can be observed at the time of initial diagnosis of lymphoma and be considered as an autoimmune manifestation. However, specific location of the lymphoma at these sites needs to be ruled out [65,68,69].

The remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome is characterized by symmetrical and acute synovitis, pitting edema, the absence of rheumatoid factor, lack of bony erosions on radiography and short clinical course. RS3PE syndrome almost exclusively affects elderly men and can occur independently, but can be associated with underlying malignancy, including lymphoma [70,71].

Adult-onset Still's disease is characterized by rash, fever and leukocytosis. Lymphadenopathy has been reported in approximately 60% of patients. Most histopathologic studies have shown nonspecific reactive hyperplasia. Its association with lymphoma is unproven and may only be the consequence of a misdiagnosis [72–74].

Eosinophilic fasciitis and the related cancer-associated fasciitis panniculitis are clinically characterized by swelling and induration of the skin of the upper or lower extremities and sometimes of the trunk. Histopathologically, septa of the subcutaneous fat tissue are thickened and inflamed. This disorder has been reported sporadically with cancer, mainly lymphoma. Fasciitis precedes the diagnosis of lymphoma by 1 year and usually is unresponsive to prednisone [75]. Differential diagnosis includes systemic sclerosis, which has been also rarely reported in association with lymphomas [76,77].

Pooled analysis of published data from Sweden, Denmark and Finland has shown that lymphoma represents the fourth cause of cancer related to dermatopolymyositis and the first cause of cancer associated with polymyositis (FIGURE 2) [78].

Renal manifestations & cryoglobulinemia

Type I cryoglobulinemia and type II mixed cryoglobulinemia are associated with a lymphoproliferative disease in 3–38% of cases, the range being dependent on HCV infection prevalence [79,80]. The overall risk of NHL in patients with HCV/mixed cryoglobulinemia is estimated to be 35-times higher than that in the general population [81]. Presence of cryoglobulinemia is suspected in the case of cold urticaria, leg ulceration, infiltrated and painful purpura, acrocyanosis, polyneuropathy, arthralgia, renal failure with proteinuria and microscopic hematuria.

In a retrospective study of 607 cryoglobulinemia cases, an association with NHL and HL was observed in 18 and two cases, respectively. Lymphoma with cryoglobulinemia belonged predominantly to the diffuse large B-cell lymphoma (DLBCL) and WM subtypes and displayed a higher frequency of primary extranodal origin, a higher rate of hepatitis C and were more frequently associated with autoimmune diseases [80].

In a study of 700 NHL and CLL, glomerulonephritis (GN) has been documented in 5%; half of them had a nephrotic syndrome and approximately a third had renal failure. GN may precede, coexist or follow the diagnosis of lymphoma by several years. The

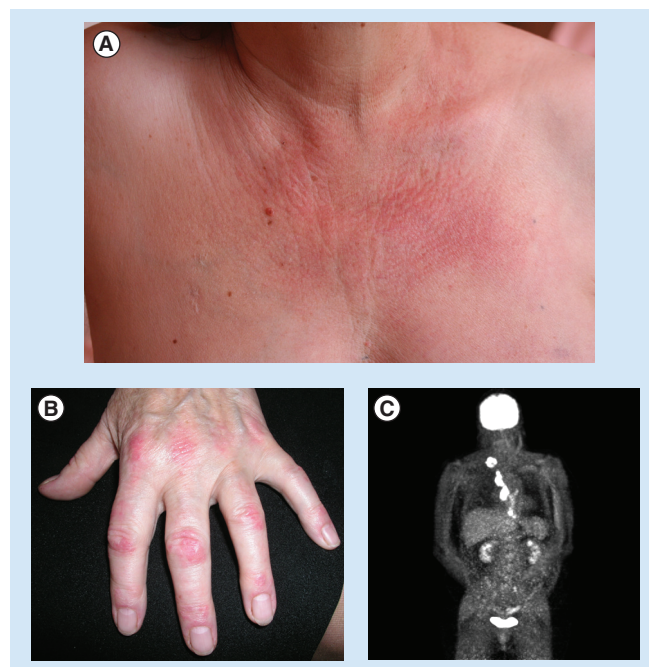


Figure 2. Polymyositis associated with a diffuse large B-cell lymphoma in a 60-year-old woman. (A)Diffuse red-purple scaling eruption of the chest. **(B)**Symmetric reddened, elevated, scaly patches over the extensor surfaces of the small joints of the hands (Gottron's sign). **(C)** Multiple mediastinal and cervical lymph nodes detected by PET imaging.

most frequent glomerular lesion is membranoproliferative GN, followed by membranous GN [77,82–84]. In addition, association between adult Henoch–Schönlein purpura, characterized by IgA linear deposit, and lymphoma can be observed less frequently [85].

Autoantibodies in lymphoma

Antinuclear autoantibodies

Except for one study concerning cutaneous T-cell NHL, and in contrast to solid tumors, it has been constantly shown that there is an increase of antinuclear autoantibody (ANA) prevalence in NHL patients in comparison with controls [86–90]. In a retrospective series of 347 untreated NHL patients, ANAs were detected by indirect immunofluorescence technique on Hep2 cells in 19% of cases compared with 5.6% in controls. In most of the cases, the nuclear immunofluorescence pattern was homogeneous (33%). Autoantibodies directed against the components of the mitotic apparatus or the mitotic-associated proteins are found in 6.9%. These antibodies were especially highly prevalent in follicular lymphoma, mantle cell lymphoma and T-cell lymphoma subtypes. The consequence and clinical relevance of the presence of ANA in the setting of lymphoma is unclear since the vast majority of patients with positive ANA did not display any autoimmune clinical symptoms and no impact on prognosis was demonstrated [86]. A similar prevalence of ANA was reported by Timuragaoglu *et al.* without any evidence of an increase in autoimmune clinical manifestations or prognosis impact [88].

In a series of 139 lymphomas (including 84 HL and 55 NHL), anti-DNA antibodies were detected in 20 patients (23.8%). Anti-RNP and anti-Sm antibodies were found in 16 (21.7%) and 14 lymphoma patients (20%), respectively, significantly more than controls (TABLE 2) [87].

Antiphospholipid antibodies

Cohort studies have suggested that the prevalence of NHL may be increased in patients with antiphospholipid syndrome [91,92]. Conversely, a high prevalence of antiphospholipid antibodies (APAs) in lymphoma patients is constantly reported. *In vitro* experiments have demonstrated that lymphoma cells can produce APAs [93,94]. Furthermore, APA titers can normalize in patients responding to lymphoma treatment, whereas non-responders retain elevated levels [95]. These observations argue strongly for a direct involvement of the lymphoma process in the autoimmune process. In a series of 90 sera from untreated and unselected lymphoma patients, anticardiolipin (aCL) antibodies and anti- β_2 -glycoprotein-I (anti- β_2 -GPI) antibodies were detected in 26.6% of cases, with a higher frequency in women and elderly patients. No correlation with the stage of the disease or the histological subtype was demonstrated. Detection of both aCL and anti- β_2 -GPI was rare (3.3%) [96]. In an Italian study including a limited number of NHL (22 patients), the aCL prevalence was 40.9% (compared with 1.7% in the control population). Concordance between aCL detection and detection of the lupus-like anticoagulant (LAC) activity was observed in only

Table 2. Frequency of autoantibodies in lymphomas.

Autoantibodies	Frequency (%)	Ref.
Antinuclear antibodies	4.6–32	[86–88,90,139]
– Anti-DNA (ss and ds)	3.5–23.8	[86–88]
– Anti-RNP	21.7	[87]
– Anti-Sm	20	[87]
Antiphospholipid antibodies	26.6–41	[96,97]
– Anti- β_2 -glycoprotein-I	26.6	[97]
– aCL	11–12.8	[97,135]
– Anti-tissue transglutaminase antibodies	10	[103]
Antineutrophil cytoplasmic antibody	2	[9]
Antibodies against cytoplasmic components (including actin, M2 mitochondria antigen, endomysium and LKM1)	18.7	[86]
Anti-thyroid antibodies	4.5	[140]
Platelet autoantibodies	8	[88]
aCL: Anticardiolipin.		

12% of cases [95]. More recently, in a series of 86 patients with untreated NHL, elevated APA levels were found in 35 patients (41%). Antibodies were mainly anti- β_2 -GPI IgM and anti- β_2 -GPI IgA. LAC activity was found in three out of 67 patients (4.5%). No significant correlation between elevated APA levels and age, sex, disease stage or grade, bone marrow involvement, B symptoms, serum lactate dehydrogenase levels, serum β_2 -microglobulin levels, international prognostic index (IPI) score, performance status, type of treatment or response to treatment was observed [97]. Despite a high prevalence, clinical relevance of APAs in lymphoma is unclear and most probably limited. With a follow-up of 14 months, Genvresse *et al.* did not observe any thrombotic events in lymphoma patients with APAs, including patients with both β_2 -GPI and aCL antibodies. By contrast, thrombosis was observed in 13.3% of patients without any APA [96]. However, arterial thrombosis occurring in patients with B-cell lymphoma with aCL and anti- β_2 -GPI antibodies has been reported and suggests that additional risk factors may facilitate clinical expression of APA [98–102]. One retrospective study reported a strong negative correlation between high APA level at diagnosis and survival. The 2-year survival was 90 months $\pm$ 5% for patients without APA at diagnosis compared with 63 months $\pm$ 11% for patients with high APA levels ($p = 0.0025$). APA was an independent prognosis factor unrelated to the IPI score. However, since prognosis impact of APA is independent of the occurrence of thrombotic event, APA prognosis value remains unclear and warrants confirmation [97].

Other autoantibodies

In an Italian series of 80 lymphoma patients, anti-tissue transglutaminase antibodies (anti-tTG) were found in approximately 10% of cases, a frequency higher than observed in the control population (0.4%) [103]. By contrast, serum anti-endomysial antibody (EmA) rate was not increased in the same population compared with controls. Positive cases harbored a normal intestinal architecture, although inflammatory infiltration of the lamina propria was observed in a few patients. No anti-tTG-positive NHL patients displayed signs of malabsorption. Conversely, all positive controls had celiac disease [103]. Presence of additional autoantibodies (serum antismooth muscle antibodies and ANAs) appears more frequently detected in anti-tTG-positive NHL [104].

Frequency, specificity and isotype of natural antibodies in sera from 60 patients with NHL was studied by an ELISA method. A high proportion of autoreactive NHL, able to recognize a large panel of antigens, was detected: 46.6% exhibited high IgG natural antibody activity, mostly against keratin, myosin and tropomyosin, 43.3% had high IgA activity against myosin, keratin and ssDNA, whereas 28.3% displayed a high IgM activity. In most cases, positive serum was polyspecific, reacting with at least two antigens. Natural antibody activity correlated with the presence of paraproteins [105].

By an indirect immunofluorescence technique on HEp2 cells, autoantibodies displaying a cytoplasmic fluorescence at the time of diagnosis of NHL before any therapy are detected in 18.7% of cases (compared with only 9% in controls). Autoantibodies are directed against cytoplasmic components, including actin, M2 mitochondria antigen, endomysium and liver kidney microsomes (LKM1) [86]. Most of them are detected in MZL [86].

It is of note that if primary thyroid lymphomas are of various histology (mainly DLBCL subtype), only MALT lymphoma, arising in patients with previous history of Hashimoto disease, display a high level of serum antithyroid antibodies [106].

The prevalence of ANCA in lymphomas has not been evaluated in large series but seems low. In a series of 140 patients with lymphoid malignancies, including CLL and myeloma, the prevalence was 3%, similar to the control population [9,107].

More recently, it has been demonstrated that patients with lymphoma or Sjogren's syndrome may produce autoantibodies against the B-cell membrane antigens CD20. Their frequency and clinical relevance remain to be determined [108].

Autoantibodies following lymphoma treatment

Fludarabine and IFN- α are drugs commonly used in the treatment of low-grade lymphomas and are well known to facilitate the occurrence of a large spectrum of autoimmune diseases [109–111].

Thyroid abnormalities, including a high frequency of elevated serum TSH levels and antithyroid antibodies are observed in association with various lymphoproliferative disorders but seem more common in patients receiving radiation therapy plus chemotherapy (FIGURE 3) [112–114].

High-dose chemotherapy followed by an autologous stem cell transplantation (ASCT) is now used widely to treat lymphoma with unfavorable prognosis factors or after relapse. It is well documented that this procedure can be associated 30–40 days following autotransplant to various autoimmune manifestations, including cytopenia, seronegative polyarthritis, GBS or thyroiditis [29,113,115–119]. Pathogenesis of autoimmune reactions and mechanisms underlying the production of autoantibodies after ASCT is not clearly understood. It was suggested that graft conditioning, infectious diseases or drugs may alter some self-antigens. Thymic damage (especially after total body irradiation) could lead to the impairment of autoreactive T-cell deletion and transient immune system imbalance characterized by impaired suppressor T-cell function, imbalance in the helper/suppressor T-cell populations have been described [120,121]. In addition, it is likely that systemic autoimmune diseases may occur in patients with predisposing factors, including certain HLA haplotypes after autologous peripheral blood stem cell transplantation [117].

Autoantibodies may occur with similar frequencies after allogenic and autologous transplantation. However, in contrast to allogenic transplant, autoantibody formation following autologous transplantation are usually transient and undetectable at 12 months post-graft [122].

Following allogenic transplant, ANAs, antismooth muscle antibodies, ANCAs, antireticulin and rheumatoid factor are frequently present and correlate with CD5⁺ B-cell counts



Figure 3. Autoimmune thyroiditis occurring 3 months after radiotherapy in a 30-year-old man with Hodgkin's lymphoma, revealed by a diffuse increased 18-fluorodeoxyglucose uptake in the thyroid gland on the PET imaging (arrow).

but do not appear to have any relationship with the occurrence of acute or chronic graft-versus-host disease (GVHD) [123].

Late-onset neutropenia (LON) following rituximab-containing chemotherapy is now a well-documented immune side effect [124,125]. Neutropenia occurs usually 3 months following rituximab infusion. Less frequently, transient severe acute thrombocytopenia and neutropenia reversible in a few days were also described suggesting a direct toxicity of rituximab rather than an immune mechanism [126,127]. LON episodes are generally self-limited without any serious infectious episodes. Intensive chemotherapy regimens, including high-dose therapy followed by ASCT, may constitute a risk factor for LON [128–130]. LON-related mechanisms remain unclear. Episodes of neutropenia are frequently associated with lymphopenia and hypogammaglobulinemia, raising the possibility that LON results from either disturbance of the balance of lymphocyte subsets or an immune dyscrasia induced by rituximab [125].

Antinuclear autoantibodies and antineutrophil autoantibodies can be detected [124,125,131]. Emergence of a T-cell population with an immunophenotype of large granular lymphocytes has been also incriminated [132]. In addition, it was recently reported that LON was related to a lack of granulopoiesis in the bone marrow, contrasting with a very high level of B-cell activating factor (BAFF), a strong stimulator of B-cell recovery, suggesting that a hematopoietic lineage competition due to an excessive B-cell recovery may promote B-cell lymphopoiesis over granulopoiesis within common developmental niches [133].

Autoimmune manifestations & lymphoma subtypes

Given the fact that most of the autoimmune disorders related to lymphoma are relatively uncommon and published mainly as case reports, an accurate prevalence of these manifestations is generally unknown. To date, a systematic assessment of autoimmune manifestations in lymphomas and their subtypes is lacking. Only the more frequent autoimmune manifestations, mainly hematological manifestations, and some lymphoma subtypes, namely MZL and AIL-T, have been prospectively or retrospectively studied in large series.

B-cell lymphoma subtypes & HL

The prevalence of autoimmune manifestations is similar in HL and NHL. However, a descriptive epidemiological study has pointed out some differences between the two groups: since in NHL autoimmunity preceded the lymphoma diagnosis (70%), it appears that the autoimmunity develops mainly after the treatment of malignancy in HL [87,134].

Regardless of the lymphoma subtype, a higher prevalence of autoimmune manifestation is constantly observed in females and correlates with the detection of a monoclonal component [135]. However, biological and/or clinical autoimmune manifestations

seem more frequent in indolent lymphoma, including follicular lymphoma, MZL and CLL/lymphocytic lymphoma, compared with aggressive lymphomas [86].

If ANAs are detected in approximately a third of follicular lymphoma and polyspecific autoantibodies are frequent, it is of note that the prevalence of clinical manifestations related to these autoantibodies is undetermined [86,136].

Clinical autoimmune manifestations in MZL are more documented [137,138]. The marginal zone is a B-cell compartment that develops around secondary follicles in secondary lymphoid organs where antigen is abundant, including the spleen, Peyer's patch and amygdalae. MZLs include MALT lymphoma and nodal MZL or extranodal-MZL (splenic MZL). Autoimmune manifestations, such as hemolytic anemia, thrombocytopenia or acquired hemostasis abnormalities, are frequently inaugural and their presence may be related to a worse prognosis [137–139]. Autoantibodies, including ANAs, thyroid autoantibodies and antisoluble antigens autoantibodies, are detected in 21.5% of gastric MALT lymphoma, a prevalence similar to control population with *H. pylori*-related gastritis [140]. However, more recently, an assessment of the clinical and genetic characteristics of MALT lymphoma arising in patients with underlying agglutinin disease, compared with patients with no agglutinin disease (including 97 extragastric diseases), showed a high prevalence of serum autoantibodies in both groups (83 and 31%, respectively) [141]. More specifically, autoantibodies directed against parietal cell antibodies and heat-shock protein 60 can be detected [135,142].

Waldenström's macroglobulinemia is frequently associated with autoantibodies and autoimmune manifestations and includes primarily neuropathy, Raynaud's phenomenon, cryoglobulinemia or cold agglutinins [143, 144].

Autoimmune complications are common in CLL, occurring in up to a quarter of all patients during the course of the illness. The most common manifestation is AIHA, followed by immune thrombocytopenia. Nonhematologic autoimmune manifestations are rare and include notably cutaneous manifestations, such as paraneoplastic pemphigus or acquired angioedema [145,146].

T-cell lymphoma subtypes

Autoimmune manifestations are frequent and polymorphous, often revealing or preceding the diagnosis by a few months, regardless of the histological T-cell lymphoma subtype [147]. AIL-T is currently considered a distinct subtype of peripheral T-cell lymphoma with specifically clinical and pathobiological features. It is suggested that AIL-T derives from follicular helper T cells. Characteristic clinical features at presentation include constitutional symptoms, lymphadenopathy, hepatosplenomegaly, serous effusions and skin rash (FIGURE 4) [148]. Biologically, patients displayed signs of B-cell hyperactivity that include hypergammaglobulinemia (but hypogammaglobulinemia can also be present during the course of the disease) with monoclonal component, Coombs-positive hemolytic anemia in



Figure 4. Skin rash occurring in a 50-year-old man with multiple lymph nodes and constitutional symptoms, related to an angioimmunoblastic T-cell lymphoma.

approximately 40% of cases and immune thrombopenia in 20% of cases. Multiple autoantibodies, such as ANA, rheumatoid factor, cold agglutinins, cryoglobulinemia and circulate immune complexes, are often detected. More specifically, smooth muscle autoantibodies reacting against vimentin, the major polypeptide of the intermediate-filament cytoskeleton of mesenchymal cells, are present in 75% of AIL-T patients [149,150].

Hepatosplenic $\gamma\delta$ T-cell lymphoma (HS $\gamma\delta$ TCL) has been recognized since 1994 [151]. Characteristic clinical features at presentation include splenomegaly and hepatomegaly, contrasting with the lack of lymphadenopathy. Marrow involvement is common and thrombocytopenia is almost constant. Cells are classically CD3⁺CD5⁻, express the $\gamma\delta$ T-cell receptor and have a nonactivated cytotoxic cell phenotype. Autoimmune cytopenia revealing the disease are usual. Chronic stimulation of the normal $\gamma\delta$ T-cell compartment by different inflammatory processes, including lupus and malaria, may be involved in the pathogenesis of this lymphoma subtype [54,151,152].

Oncogenic anaplastic lymphoma kinase (ALK) fusion proteins (including nucleophosmin–ALK and other variants) are expressed in many cases of anaplastic large-cell lymphoma (ALCL) [153]. It has been shown that ALCL patients constantly develop antibodies against the oncogenic fusion kinase nucleophosmin (NPM)–ALK. The presence of anti-ALK antibodies may be clinically relevant and explain the relatively good prognosis of ALK-positive ALCL [153,154].

Pathogenic hypothesis

The lymphoma proliferation is issued from CD5⁺ autoreactive B cells. The CD5⁺ B-cell population, constituting approximately 20% of splenic and circulating B cells, is prominent in early life and produces low-avidity and, thereby, polyreactive antibodies. CD5⁺ B cells appear to be involved in the autoantibody production in autoimmune disease and are

particularly susceptible to transformation in lymphoproliferative disorders. This autoreactive repertoire secrete the so-called natural autoantibodies characterized by their broad reactivity mainly directed against very well-conserved public epitopes. They fulfil the definition of an autoantibody since they are self-reactive, but they are not self-specific. The way by which this autoreactive B-cell repertoire frequently undergoes malignant transformation is still unrecognized. It has been postulated that the continuous challenge of this autoreactive repertoire by self-antigens could favor malignant transformation [155,156].

This hypothesis can be applied to CD5⁺ B-cell lymphomas, including mantle cell lymphomas and lymphocytic lymphomas, which effectively usually display a high rate of autoimmune manifestations. However, B-cell lymphomas are predominantly CD5 negative, such as follicular lymphoma, and are still able to produce autoantibodies against self-antigens, suggesting a loss of CD5 expression during lymphomagenesis [136].

Molecular analysis of V genes in lymphoma strongly argues for the transformation of an autoreactive B-cell. For instance, CDR3 sequence and adjacent regions of immunoglobulin genes from B-cell lymphoma of MALT display 60–81% homology with autoantibody-associated lymphocyte clones, including rheumatoid factor [157].

V_H4-34 (V_H4-21), a member of the V_H4 family, appears selectively to encode immunoglobulins with autoantibody activity, particularly anti-red cell antibodies. The pattern of usage of this V_H gene by B-cell tumors demonstrates clear asymmetry among different tumor types. Approximately 15% of NHL express V_H4-34 , compared with only 3% in CD5⁺ CLL [158,159]. Conversely, its quasi constant absence in multiple myeloma may explain the rarity of autoimmune manifestations (and especially AHAI) in this setting [160].

Nonlymphoma cells may produce autoantibodies

Detection of multiple autoantibodies directed against distinct antigens suggests that some of them are not exclusively produced by the tumoral clone and are rather the consequence of a more general disordered immunoregulation [93,161].

This phenomenon is likely to explain autoimmunity in T-cell lymphoma, especially in AIL-T. In addition, autoimmune manifestations occurring in HL are likely to be the consequence of an altered immunoregulation since Reed–Sternberg cells are not able to produce antibodies.

The role of Tregs in lymphoma-related autoimmune manifestations remains unclear. Tregs prevent autoimmune diseases by suppression of self-reactive T cells and also suppress the immune response against cancer. Tregs are over-represented in biopsy specimens of B-cell NHL and it has been demonstrated that B cells are involved in the recruitment of these cells into the area of lymphoma [162]. Whether a Treg population that modulates the immune response against lymphoma cells may also be involved in the occurrence of autoimmune manifestations remains to be demonstrated.

Chronic stimulation by viral antigen may facilitate both lymphomagenesis & autoimmunity

The role of infectious agents, such as *H. pylori* and HCV in the emergence of lymphoma is well established. It has been hypothesized that lymphocyte chronic stimulation may lead to the emergence of autoreactive lymphoma cells [163].

HCV-related lymphomas are mainly indolent, including MZL and lymphoplasmacytic lymphoma [164]. In addition to type II mixed cryoglobulinemia, autoimmune manifestations in HCV-related lymphoma are frequent and various. The expression of a restricted repertoire of immunoglobulin V_H and V_L genes, V_HI-69 and V_KA27 by HCV-associated lymphoma B-cells, as a consequence of E2 antigenic stimulation, may be involved in the emergence of frequent immune disorders [165,166]. Interestingly, increased expression of CD81 on innate B cells, a population that is expanded in the liver and peripheral blood of chronic HCV-infected patients, suggests a role in viral specific activation and clonal proliferation in chronic HCV infection [167].

In addition to V gene usage, some cytokines, involved in B-cell terminal differentiation, such as IL-6, may facilitate antibody production and immune manifestations. For instance, lymphoma cells issued from patients with immune thrombocytopenia and cultured with IL-6 are able to differentiate to lymphoma cells producing IgM-type antiplatelet antibodies. IL-6 production can be the result of both autocrine and paracrine mechanisms [57,93].

Autoimmunity as a consequence of alteration of the Fas/Fas-ligand pathway

Fas (APO-1/CD95) is a cell-surface receptor involved in cell-death signaling. Fas mutations were previously reported as the genetic defect responsible for human lymphoproliferative syndrome associated with autoimmune manifestations (also known as autoimmune lymphoproliferative syndrome or Canale-Smith syndrome). This syndrome includes polyadenopathies, splenomegaly, and frequent autoimmune manifestations, such as immune cytopenia, skin rash, uveitis or arthritis. Symptoms are detected during the neonatal period and usually decrease over time [93,168]. Prevalence of lymphoma is

increased in this population and several reports have highlighted the high frequency of autoantibodies in lymphomas related to autoimmune lymphoproliferative syndrome [169–171]. Interestingly, acquired somatic mutations of Fas are observed in 11% of NHL and seem particularly prevalent in MALT lymphomas and lymphomas with autoimmune manifestations [172]. Furthermore, interplay between the Fas/Fas-ligand apoptosis pathway and self-antigen recognition by lymphoma B cells has been recently demonstrated in a Burkitt cell line model. It has been shown that Fas-mediated apoptosis was inhibited upon surface IgM engagement by the self erythrocyte 'i' antigen for which the malignant clone has affinity [173]. Physiopathological hypotheses are summarized in FIGURE 5.

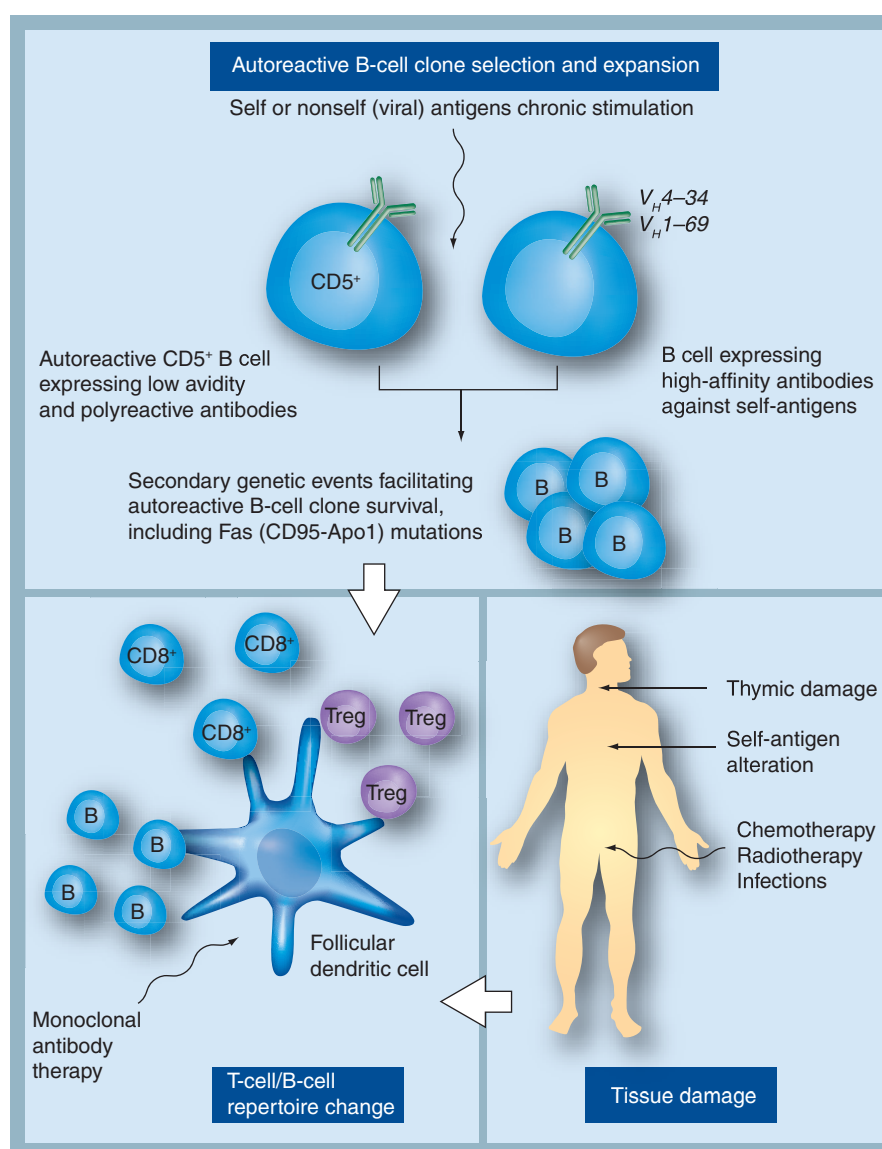


Figure 5. Hypothetical mechanisms leading to the development of autoimmune manifestations in lymphoma.

Expert commentary & five-year view

Lymphomas and autoimmune manifestations may constitute two faces of the same process. In some cases, a pure immuno-suppressive treatment, based on cyclosporin can be effective for treating AIL-T [174]. Conversely, chemotherapy alone or combined with rituximab can ameliorate related-lymphoma autoimmune manifestations [175]. Rituximab, a monoclonal antibody directed against CD20 antigen is now widely used to treat B-cell lymphomas and a large variety of autoimmune diseases, including SLE, RA, pSS or autoimmune cytopenia [176]. Rituximab is now considered as the cornerstone to treat lymphoma-related autoimmune manifestations. Encouraging results have been obtained in cryoglobulinemia, leading to an improvement of skin vasculitis manifestations (ulcers, purpura or urticaria), subjective symptoms of peripheral neuropathy, arthralgias and fever [177]. Importantly, HCV infection is not a contraindication to use rituximab, which appears to be highly effective without any significant toxicity in this context [178]. Favorable results have been also obtained in AHAI with cold agglutinins [179,180].

The precise mechanisms of action in autoimmunity remain to be fully clarified and clearly represent a key issue to use monoclonal antibodies more rationally in this setting. The main hypotheses include Fc receptor saturation of reticuloendothelial cells by CD20⁺ opsonized cells, a decrease of autoantibodies, the destruction of antigen presenting B cells or a shift of the B-cell repertoire. However, some patients, despite a very low B-cell count, can have persistent autoimmune manifestations, suggesting that T-cell immunity is involved in the autoimmune process. Other monoclonal antibodies may have potential interest to treat autoimmune manifestations in relation to lymphoma. They include Campath-1H (anti-CD52) [181], epratuzumab (anti-CD22), anti-CD154, BAFF inhibitors or daclizumab (a humanized monoclonal antibody against IL-2 that can

inactivate the cytokine/receptor complex) [182,183]. Development of murine models which display both lymphoma and subsequent autoimmune manifestations may be helpful in the near future to understand further the inter-relationship which links lymphoma and autoimmunity [184].

The effect on tumor biology of 'paraneoplastic' autoimmune reactions remains mainly unknown and represents another future prospect. The presence of ANAs was correlated to a better prognosis in non-small-cell lung cancer and in colorectal adenocarcinoma [185,186]. In mice, ANAs directed against nucleosome antigens suppressed T-cell lymphoma development and increased survival, suggesting that autoantibodies may have an anti-tumor effect and represent a mechanism of immune surveillance against tumors [187–189]. Some autoantibodies, such as ANA directed against centromere protein F, are detected in carcinomas but also in lymphoma, indicating that autoantibodies represent an unspecific and more general mechanism of immune surveillance against tumors [190]. However, to date, no prospective study has demonstrated any favorable prognosis impact of the presence of autoantibodies in lymphoma.

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Key issues

- Development of lymphoma during the course of autoimmune and chronic inflammatory conditions is well known. Similarly, development of clinical or biological signs of autoimmunity at the time of the initial diagnosis of lymphoma or during its course represents the other end of the spectrum of the inter-relationships linking lymphoproliferative malignancies and autoimmune diseases.
- The spectrum of clinical autoimmune manifestations related to lymphoma includes mainly skin diseases, PNS and CNS involvement, hematological manifestations, rheumatic diseases and renal lesions.
- A high prevalence of antibodies, including antinuclear antibodies, antiphospholipid antibodies or endomysium antibodies, is observed in lymphoma but usually without clinical expression.
- Autoimmune manifestations are observed in all lymphoma subtypes but are particularly prevalent in marginal-zone lymphoma and T-cell lymphoma. However, a systematic assessment of autoimmune manifestations in lymphomas and their subtypes is lacking to provide an accurate frequency of the association.
- The prognosis value of autoimmune manifestations in lymphoma is undetermined.
- The physiopathology of the immune manifestations may involve production of autoantibodies by natural CD5⁺ autoreactive B cells, a loss of immune tolerance, an abnormality in the Fas/Fas-ligand pathway or a chronic antigenic (viral) stimulation.
- Monoclonal antibodies (including rituximab, Campath-1H or epratuzumab) constitute the most promising approach to treat lymphoma-related immune disorders in combination with treatment of the underlying lymphoma.

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