Review

Hematologic manifestations of connective autoimmune diseases

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ABSTRACT

Autoimmune connective tissue diseases (ACTDs) constitute a heterogeneous group of chronic immune-mediated inflammatory disorders, primarily affecting connective tissues and usually characterized by multisystem involvement with variable and frequently overlapping clinical manifestations. Abnormal immune regulation patterns and persistent inflammation are ACTD hallmarks. In such a context, autoimmunity/inflammation-associated cellular and molecular networks drive a complex of reactions that may involve hemopoietic tissue and peripheral blood cells. Hematologic abnormalities affecting one or more cellular lineages are frequent manifestations of ACTDs, and may represent an important prognostic factor, reflecting the rate of activation of autoimmune/inflammatory processes. Moreover, an increased frequency of hematologic malignancies, mainly lymphoproliferative disorders, has been observed in ACTDs, such as Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and polymyositis/dermatomyositis. A proliferative drive likely constitutes the link between chronic immune activation/dysregulation and malignant transformation, creating an increased risk for genetic aberrations that may lead to uncontrolled clonal proliferation. Revealing the nature of lymphomagenesis in relation to autoimmunity/inflammation will allow the identification of subjects at risk in order to select the appropriate diagnostic and therapeutic options. In this paper, the main hematologic manifestations of adulthood ACTDs are reviewed and discussed.

Introduction

Autoimmune connective tissue diseases (ACTDs) encompass a heterogeneous group of chronic immune-mediated inflammatory disorders, primarily affecting connective tissues and usually characterized by multisystemic involvement and variable and frequently overlapping clinical manifestations.

A complex interaction among genetic predisposing factors, endocrine *status*, and environmental triggering agents is likely involved in their etiopathogenesis. Abnormal immune regulation patterns and persistent inflammation are ACTD hallmarks (1). In such a context, autoimmunity/inflammation-associated cellular and molecular networks drive a variety of reactions that may involve hematopoietic tissue and peripheral blood cells. Thus, hematologic abnormalities affecting one or more cellular lineages are common in ACTDs, and may also represent a prognostic variable, reflecting the autoimmune/inflammatory activation.

In this regard, systemic lupus erythematosus (SLE) is the ACTD archetype, showing a particularly high frequency of hematologic manifestations (2), which have been included in the revised criteria for the SLE classification by the American College of Rheumatology (ACR) (3).

Moreover, considerable attention has been directed to the association of hematologic malignancies and ACTDs, likely related to the chronic systemic stimulation of the immuno-inflammatory system and to common genetic/environmental factors.

The main hematologic manifestations of adulthood ACTDs are herein reviewed and discussed.

Methods

A detailed search of the available literature was performed in the PubMed database (United States National Library of Medicine), using the following key words: autoimmune connective tissue diseases (and relative syndromal names), hematologic manifestations, hematologic abnormalities, cellular quantitative disorders, anemia, leuko-

penia, lymphopenia, thrombocytopenia, bicytopenia, pancytopenia, marrow fibrosis, myelodysplastic syndromes, thrombocytosis, leukocytosis, lymphocytosis, monocytosis, eosinophilia, hematologic malignancies, lymphoproliferative disorders.

Results

Anemia

Anemia, defined as reduced levels of hematocrit and/or hemoglobin (Hb), encompasses different variants that may recognize an autoimmune or non-autoimmune pathogenesis (Table I).

Due to ACTDs associated persistent immune activation, it is not surprising that the most common variant observed in these patients is anemia of chronic disease (ACD), which recognizes a primarily cytokine-driven pathogenesis (4) (Table II). Moreover, an ACD component often coexists with other types of anemia diagnosed in patients affected by ACTDs (4).

ACD is usually a mild to moderate normocytic normochromic or, less frequently, microcytic hypochromic anemia, defined by hypoferremia, normal or decreased transferrin levels, reduced transferrin saturation, normal/elevated serum ferritin, normal or reduced reticulocytes, adequate/increased reticuloendothelial system (RES) iron stores, and iron-restricted erythropoiesis, in the presence of normal bone marrow (BM) myeloid/erythroid *ratio* (4).

Anemia, the most common extra-articular manifestation of rheumatoid arthritis (RA), is associated with a negative impact on both patient symptoms and quality of life (5). Moreover, anemic patients were reported to show more severe disease than nonanemics (6, 7).

In a recent review of the literature, the prevalence of anemia has been found to range from 33% to 60% in RA (8). In a large patient cohort, using the World Health Organization definition, the current prevalence of mild anemia (Hb <12 g/dL for females and <13 g/dL for males) was 31.5% for both sexes, 3 times the rate in the general population, while the lifetime anemia prevalence was 57% (9). However, severe chronic anemia (Hb <10 g/dL) was infrequent (3.4%), with a lifetime prevalence of 13.7% (9).

In RA of recent onset, mild severity anemia was found to develop in 64% of patients, predominantly within the first year, and was classified as ACD in 77%, and as iron deficiency anemia (IDA) in 23% of the anemic subjects, with frequent overlap (6).

ACD and IDA are widely reported as the most common variants in RA (5-7, 10, 11), whereas pernicious anemia (PA) (12, 13), pure red cell aplasia (PRCA) (14-17), hemolytic anemia (HA) (18, 19), or sideroblastic anemia (SA) (20) are infrequent. Aplastic anemia (AA) has been mostly reported as a drug-related side effect (21, 22).

Anemia is a common morbidity in SLE, observed in about 38-52% of patients (23-25), frequently as disease presenting symptom (26).

Anemia emerged as a hematologic manifestation strongly associated with disease activity and with early and late damage accrual during the SLE course (27), being also identified as a disease flare (28) and mortality (29) predictor.

ACD is the most common variant in SLE patients, with a prevalence ranging from 37% to 73% in different studies (23, 25, 26, 30); the second in order of frequency is IDA, reported with a prevalence of 36% (23).

HA, included among the ACR hematologic criteria for SLE classification (3), shows a prevalence ranging from 7 to 28% (23, 25-27, 31-34), often representing the SLE initial manifestation (26, 32, 34).

HA prevalence was found to be similar in childhood-, adult-, and late-onset groups of SLE patients at the time of diagnosis, (22%, 20%, and 23%, respectively), however, its cumulative frequency over time was lower in the adult group (20%), compared to childhood and elderly onset patients (32% in both) (34).

In SLE patients, HA is frequently associated with the presence of circulating antiphospholipid antibodies (aPL) (31, 33, 35, 36), and positively related to renal involvement (2, 32). HA has been

Table I. Pathogenesis of anemia in autoimmune connective tissue diseases.

Nonautoimmune
Anemia of chronic disease
Iron deficiency anemia
Anemia of chronic renal failure
Sideroblastic anemia
Marrow erythroid hypoplasia
Drug toxicity
Autoimmune
Autoimmune hemolytic anemia
Pure red cell aplasia
Aplastic anemia
Pernicious anemia
Autoimmune dyserythropoiesis
Drug-induced hemolytic anemia

Table II. Cytokines in the pathophysiology of anemia of chronic disease (4).

Cytokine	Action	Effect
TNF-α	inhibits proliferation and differentiation of erythron	mpaired erythropoiesis
	inhibits the EPO production	impaired erythropoiesis
	impairs the response to EPO of progenitor cells	impaired erythropoiesis
	induces ferritin transcription	diversion of iron traffic
	decreases erythrocyte life span	erythrophagocytosis
IFN-γ	inhibits proliferation and differentiation of erythron	impaired erythropoiesis
	reduces the EPO production	impaired erythropoiesis
	downregulates ferroportin expression	diversion of iron traffic
IL-1	inhibits proliferation and differentiation of erythron	impaired erythropoiesis
	inhibits the EPO production	impaired erythropoiesis
	induces ferritin transcription	diversion of iron traffic
IL-6	induces ferritin transcription	diversion of iron traffic
	stimulates hepatic hepcidin production	diversion of iron traffic
IL-10	induces ferritin transcription	diversion of iron traffic
	enhances RES transferrin-receptor expression and iron uptake	diversion of iron traffic

TNF-α: tumor necrosis factor-α; EPO: erythropoietin; IFN-γ: interferon-γ; IL-1: interleukin-1; IL-6: interleukin-6; IL-10: interleukin-10; RES: reticuloendothelial system.

proposed as an index of disease activity (25) and a predictor of poor survival (37-39).

Other types of anemia, such as PA (23, 40), SA (41), microangiopathic hemolytic anemia (MHA) (42-44), or PRCA (45-49) are uncommon in SLE. In a limited number of SLE patients, AA, mostly due to drug toxicity, may be primarily attributed to the underlying disease (50-54).

In a series of 380 patients with primary Sjögren's syndrome (pSS), anemia (defined as Hb <11 g/dL in both genders) was found in 20%, and severe (Hb <9 g/dL) in only 4%, consistent with the results of previous studies globally reporting anemia in 21% of pSS patients (55).

ACD is the most common variant, whereas HA (55-60), AA (55, 56, 61-63), PA (64, 65), and PRCA (56, 66-68) are infrequent. Recently, the development of PRCA combined with HA was reported in a pSS patient (69).

Anemia has been reported to be a predictor of unfavourable prognosis in systemic sclerosis (SSc) (scleroderma) (70-72). In a cohort of SSc patients, the anemia prevalence was 25% (73). In this disease, the most common variant was ACD (73, 74), while HA (75, 76), MHA (77), and PA (78) have been rarely observed.

Anemia is a common hematologic manifestation of mixed connective tissue disease (MCTD), and comprised as minor criterion in the Sharp diagnostic criteria set for the disease classification (79).

In patients suffering from antiphospholipid syndrome (APS), the prevalence of HA was 10.4% in primary APS (pAPS) (80) and of 28.6% in secondary APS (sAPS) (81). In a cohort of 1,000 APS patients, HA had a cumulative frequency of 9.7%, being the disease presenting manifestation in 6.6% of cases (82).

A highly significant association was found between HA and other APS manifestations, such as *livedo reticularis* and cardiac valve abnormalities (80, 83).

In patients with relapsing polychondritis (RP), mild to moderate anemia is a common manifestation (84), with an estimated frequency of 50% at the disease onset, and a cumulative frequency of 55% over time (85). In RP patients, the most commonly observed variant is ACD (84), while HA (86, 87) or PA (88) are rare. Importantly, the presence of anemia at diagnosis was found to be a marker for decreased survival in RP patients, irrespective of their age (85).

Leukopenia

In ACTDs, leukopenia (defined as total peripheral white blood count <4,000/mm^3) may be related to immune- or non-immune-mediated mechanisms (Table III).

Leukopenia, included in the ACR hematologic criteria for SLE classification (3), is a common manifestation, reported in 20-64% of patients (25, 26, 30, 89, 90); however, severe leukopenia (<2,000/mm^3) is infrequent (91).

In a study of 285 new-onset SLE patients of different ages, pediatric patients exhibited leukopenia (40%) more frequently than adult (15%) and elderly (23%) ones (34).

Of note, leukopenia *per se* was not identified as the major cause of increased susceptibility to infections, that was mainly related to the SLE treatments (in particular to glucocorticoid therapy) (31). Moreover, in a cohort of 408 patients, over a median duration of follow-up of 11 years, leukopenia was reported to be a protective factor against the risk of SLE-related mortality (37).

Consistent with the results of previous studies globally reporting a leukopenia frequency of 17%, in a series of 380 pSS patients the incidence of moderate leukopenia was 16%, being severe in only one case (0.2%) (55). In univariate analysis, leukopenic pSS patients presented a higher prevalence of peripheral neuropathy, anti-Ro/SS-A and anti-La/SS-B antibodies, rheumatoid factor (RF), cryoglobulinemia, and hypocomplementemia than those without leukopenia, although only anti-Ro/SS-A and RF resulted significant independent variables in the multivariate analysis (55).

Leukopenia is a common hematologic manifestation of MCTD, comprised as minor criterion in the Sharp set of disease classification criteria (79), and as SLE-like finding in the Kasukawa set (92).

In a cohort of 1,000 APS patients, leukopenia was significantly more frequent in sAPS than pAPS patients (38% *vs.* 2%), suggesting that factors other than aPL may play a pathogenetic role (82).

Table III. Pathogenesis of leukopenia in autoimmune connective tissue diseases.

Antibody-mediated peripheral leukocyte destruction
Antigranulocyte, antilymphocyte, antimonocyte autoantibodies
Peripheral sequestration
Hypersplenism
Increased margination
Dysregulated apoptosis
Bone marrow dysfunction
Depressed hematopoiesis due to humoral or cell-mediated autoimmunity
Maturation arrest
Inadequate mobilization response
Drug-related bone marrow failure

Kikuchi-Fujimoto's disease

Leukopenia is a frequent finding (about 50% of cases) in the setting of Kikuchi-Fujimoto's disease (KFD) or histiocytic necrotizing lymphadenitis (93). KFD is a clinicopathological entity of unknown etiology, constituting a rare and usually self-limiting cause of lymphadenopathy, frequently associated with the presence of constitutional symptoms, arthralgia and skin rash, features resembling SLE (93, 94). The KFD diagnosis is based on the characteristic histologic changes in lymph nodes consisting of paracortical necrosis and mononuclear infiltrates lacking neutrophils and plasma cells (93, 94).

Interestingly, KFD has been described in association with SLE (95-100), undifferentiated CTD (100), and catastrophic APS (101).

Neutropenia

Neutropenia (neutrophil count <1,500/mm^3) coexisting with splenomegaly and RA are distinct features defining Felty's syndrome (FS), a rare RA variant (<1%) with peculiar extra-articular manifestations and genetic linkage (90% of FS patients carry human leukocyte antigen DR4) (102). In FS, neutropenia appears to be immunologically mediated, with the involvement

of different cellular and humoral immune mechanisms, leading to a complex interplay of defects in neutrophil production, distribution, destruction, and apoptosis (103).

FS neutropenia is usually chronic, frequently severe, and often associated with a substantial morbidity related to recurrent infections. As a matter of fact, bacterial infections are the main cause of the increased mortality observed in these patients (102).

In SLE patients, neutropenia is a common hematologic manifestation, with a prevalence ranging from 20 to 47% (30, 31), however, severe neutropenia or agranulocytosis (absolute neutrophil count <500/mm^3) are quite rare (91, 103-106).

Neutropenia in SLE is likely immune-mediated since antineutrophil autoantibodies have been frequently detected (107), although without a clear correlation with neutropenia, whose development likely requires more complex mechanisms (103).

Neutropenia usually has a little impact on SLE course, and does not significantly increase the risk of infectious complications (103).

In a large cohort of pSS patients, neutropenia was observed in 7% of cases (55). pSS neutropenia is generally mild, not requiring therapy; severe neutropenia or agranulocytosis are uncommon (59, 108-111).

In a series of agranulocytic pSS patients, no serious infections have been found after a mean follow up of 34.8 months (111).

The pathogenesis of pSS neutropenia/agranulocytosis is likely immune, and both humoral and cellular mechanisms have been suggested to affect BM granulopoiesis and/or mediate neutrophil peripheral destruction (110).

Neutropenia was found to occur more frequently in sAPS than in pAPS patients (112).

Lymphopenia

In RA patients, lymphopenia (lymphocyte count <1,500/mm^3) has been observed with a frequency ranging from 15 to 30% (113, 114).

Lymphopenia is one of the most common hematologic SLE manifestations, listed among the ACR criteria for the disease classification (3). It has been reported with a prevalence ranging from 20% to 82% (30, 31, 34, 115).

Comparing pediatric-, adult- and elderly-new-onset SLE patient groups, the prevalence of lymphopenia was similar at the time of diagnosis (44%, 43%, and 36%, respectively) and during the disease course (72%, 77%, and 77%, respectively) (34).

In a multiethnic longitudinal outcome study entailing 591 adult SLE patients, lymphopenia was associated with several clinical/immunologic manifestations, such as renal involvement, leukopenia, thrombocytopenia, high anti-dsDNA antibody levels and anti-Ro/SS-A antibodies, early and during the disease course, while it was negatively related to photosensitivity (115). Furthermore, owing to moderate, and overall marked lymphocytopenia strongly correlated with higher disease activity and damage accrual, the lymphocyte count was suggested to be a good and inexpensive biomarker to monitor disease activity (115).

In a large series of pSS patients, lymphopenia was found in 9% (55). In univariate analysis, lymphopenic patients showed a higher frequency of renal involvement and anti-La/SS-B antibodies, both representing significant independent variables in the multivariate analysis (55).

Lymphocytopenia was significantly more frequent in patients with sAPS (75%) than in patients with pAPS (41%) (116).

In dermatomyositis (DM), lymphopenia is a common hematologic manifestation (117, 118), with a prevalence of 85% in untreated patients, affecting all lymphocyte subsets, although the most striking alterations involve the CD8$^+$ T cell lineage (118).

CD4$^+$ T-lymphocytopenia

CD4$^+$ T-lymphocytopenia, mainly due to the decrease of the CD4$^+$/CD45RA$^+$ subpopulation, has been reported in about 5% of pSS patients (119). Dysregulated apoptosis is likely involved in its pathogenesis, whereas the role of antibodies against CD4$^+$ T cells is unclear (120). Absolute CD4$^+$ T-lymphocyte counts have been found to be significantly lower in anti-Ro/SS-A seropositive pSS patients than in seronegative ones (121).

CD4$^+$ T-lymphocytopenia has been also reported in pAPS patients (122, 123).

Thrombocytopenia

In ACTDs , thrombocytopenia (platelet count <100,000/mm^3) may be immune- or non-immune-mediated (Table IV).

In RA patients, thrombocytopenia was mostly reported as a drug-induced effect and uncommonly related to the disease itself (124-126). Otherwise, thrombocytopenia is a frequent hematologic feature in the setting of FS (127).

In SLE patients, thrombocytopenia is a common manifestation, comprised among the ACR hematologic criteria for the disease classification (3). Peripheral platelet aggregation/destruction due to specific autoantibodies, anti-thrombopoietin (TPO) antibodies, low effective circulating TPO levels, and impaired compensatory megakariopoiesis are mechanisms likely involved in its pathogenesis (128).

In SLE patients, the thrombocytopenia prevalence ranges from 8 to 31% (31, 34, 36, 129-131), whereas severe thrombocytopenia (platelet count <50,000/mm^3) is relatively infrequent (~5%) (30, 33). The association of thrombocytopenia with the presence of aPL (33, 129, 131), and antibodies against double stranded deoxyribonucleic acid (anti-dsDNA) has been frequently reported (129, 131).

At disease presentation, thrombocytopenia had a significantly higher

Table IV. Pathogenesis of thrombocytopenia in autoimmune connective tissue diseases.

Non-autoimmune
Impaired or ineffective bone marrow thrombopoiesis
Low effective circulating thrombopoietin levels
Peripheral platelet dilution, sequestration or consumption
Autoimmune
Humoral and cell-mediated specific autoimmunity
Antithrombopoietin antibodies
Antiphospholipid antibodies

prevalence in pediatric SLE patients (34%) than in adult (12%) and elderly (14%) ones, whereas, during the disease course, no significant differences were observed among the 3 groups of patients (36%, 25%, 32%, respectively) (34).

In several studies, thrombocytopenia emerged as a major indicator of cumulative morbidity affecting overall prognosis (130, 132), and a major predictor of SLE mortality (31, 37, 129, 133-136). The contribution of thrombocytopenia to a poorer survival in SLE is not primarily due to bleeding complications, but mainly depends on its association with more aggressive disease (129, 130, 132), and in particular with both HA (136) and renal involvement (33, 129, 130, 132, 136).

Furthermore, thrombocytopenia was found to identify families with a severe SLE phenotype, revealing specific genetic linkages (131).

In a series of 380 pSS patients, thrombocytopenia of mild, moderate, and severe degree was found in 13%, 3%, and 0.4% of cases, respectively, according to the cumulative prevalence of 11% detected in previous studies involving 643 patients (55). Thrombocytopenic patients presented a higher prevalence of renal involvement and anti-La/SS-B antibodies in the univariate analysis, being both significant independent variables in the multivariate analysis (55).

Thrombocytopenia is a common hematologic manifestation of MCTD, comprised as minor criterion in the Sharp set of disease classification (79), and as SLE-like finding in the Kasukawa set (92).

Thrombocytopenia is a frequent hematologic manifestation of APS, comprised among the Harris disease classification criteria (137). In APS patients, thrombocytopenia prevalence was found to range from 20 to 30% (82, 138-140), being higher in sAPS than in pAPS (43% *vs*. 21%) (82).

In a cohort of 1,000 APS patients, thrombocytopenia had a cumulative frequency of 29.6%, representing the disease initial manifestation in 21.9%, of cases (82).

APS thrombocytopenia is generally mild, rarely associated with bleeding complication, usually not requiring treatment (139, 141, 142). However, it was found to represent a risk factor for cardiac, neurological, cutaneous, and articular involvement (140, 143).

Severe thrombocytopenia was reported with a frequency of about 3-10% (138, 139). In patients with APS-associated refractory thrombocytopenia, splenectomy usually provides a good and long-term response (141, 144).

Bicytopenia/Pancytopenia

ACTD patients may present blood cell quantitative disorders affecting more than one cellular lineage (bicytopenia/pancytopenia) (55, 108, 145, 146), as a consequence of immune or non-immune pathogenetic mechanisms, including underlying autoimmunity, dysregulated apoptosis (147, 148), hemophagocytosis (149), drug toxicity (150), marrow fibrosis (MF), myelodysplastic syndromes (MDS), BM necrosis or gelatinous transformation (146, 151-155).

Evans' syndrome

Autoimmune bicytopenia entailing the simultaneous or sequential occurrence of HA and thrombocytopenia defines the Evans' syndrome, a relatively rare hematologic condition which has been described as primary or in association with lymphoproliferative disorders (LPDs) and ACTDs, such as SLE (156-158), APS (159), and DM (160, 161).

Thrombotic thrombocytopenic purpura

Bicytopenia constitutes a cardinal feature in the setting of thrombotic microangiopathic hemolytic anemia or thrombotic thrombocytopenic purpura (TTP). TTP is a severe microvascular occlusive "thrombotic microangiopathy", characterized by MHA (as indicated by erythrocyte fragmentation on peripheral blood smears), profound thrombocytopenia, and systemic platelet aggregation, in the presence of fever and variable degrees of tissue/organ ischemia (162).

TTP may be primary or secondary to drug therapy, BM/organ transplantation, and autoimmune diseases (162). TTP is a life-threatening hematologic condition, requiring early recognition and prompt institution of effective treatment, including plasmapheresis that may dramatically improve the outcome (42, 162, 163).

TTP etiopathogenesis is unclear. Endothelial cell damage or apoptosis, decreased activity of von Willebrand factor-cleaving metalloprotease (*i.e.* ADAMST-13), presence of immunocomplexes or autoantibodies, such as aPL, may be involved in the TTP development (164).

TTP has been described in SLE patients (42,163,165-168) with a substantially higher prevalence than in the general population (4-11 cases per million) (168). The TTP clinical presentation may occur before (73%) SLE onset, simultaneously (12%), or subsequently (15%) (166, 167). TTP has been rarely reported in SSc (169-171) or MCTD (172-175), and occasionally in DM (176, 177), polymyositis (PM) (178), or RA (179).

Moreover, TTP has been documented in APS patients (164, 180, 181), frequently as initial manifestation of the disease (164).

Hemophagocytosis

In ACTDs, bicytopenia/pancytopenia may be related to hemophagocytosis (149). Reactive hemophagocytic syndrome (HS) is a rare but life-threatening hematologic condition, mainly observed in the setting of serious infections or LPDs, and characterized by peripheral cytopenias and BM RES infiltration by non-malignant, mature-looking histiocytes that undergo uncontrolled hemophagocytosis (182).

HS has been reported in RA (149, 183-187), occasionally in MCTD (188), SS (149), SSc (149, 189), and DM (149,190,191), but the highest frequency was observed in SLE patients (99, 149, 192-196). In the majority of these reports, HS was the SLE presenting manifestation. Moreover, in long term SLE studies HS seems to define a severe disease subset, characterized by repeated flares, possible HS recurrences, and requirement of prolonged immunosuppression (99).

In ACTD patients, anemia and thrombocytopenia were found to be the most significant hematologic factors associated with the HS-related mortality (99, 149).

Marrow fibrosis

In patients with ACTDs, bicytopenia/pancytopenia may be related to MF, a rare BM disorder with the resulting features of myelophthisis, likely due to cytokine fibrogenic effects (197).

MF is a pathologic condition characterized by collagen type I and III deposition by non-neoplastic fibroblasts representing a feature distinct from chronic idiopathic myelofibrosis, which is a clonal myeloproliferative disease.

MF may occur in the setting of neoplastic disorders involving BM, including myeloid and lymphoid malignancies, severe infections, or ACTDs, especially SLE, of which MF may represent the initial manifestation (198-209).

MF has been occasionally described in pSS (208,210), SSc (202, 211), and DM (212, 213) patients.

Myelodysplastic syndromes

MDS are clonal hematopoietic stem cell disorders, characterized by ineffective dysplastic hematopoiesis, leading to the contradictory phenomena of normal/increased BM cellularity concurrent with peripheral cytopenias, as well as by a substantial risk of malignant progression (214).

Several reports described MDS occurring simultaneously or in a close temporal relationship with RP (85, 215-221) so that about 30% of RP cases have been found to be associated with MDS (222). The occurrence of MDS in patients with pSS (223, 224), SLE (223), and DM (225) was occasionally reported.

Bone marrow necrosis

BM necrosis is a rare condition due to BM ischemia depending on alteration of the local microcirculation. It may be associated with malignancies, infections, sickle cell disease, and ACTDs, such as SLE (151-153) and APS (154, 226, 227).

Bone marrow gelatinous transformation

In conditions such as cachexia due to malignancies, anorexia nervosa, or other chronic illnesses, BM may undergo gelatinous transformation, a rare disorder characterized by fat atrophy and cellular hypoplasia. This phenomenon has been occasionally reported in SLE patients presenting peripheral pancytopenia (146, 155).

Leukocytosis

In the absence of infections, disease relapses or glucocorticoid therapy, patients with ACTDs infrequently show elevations in leukocyte count (228).

In a cohort of 180 SSc patients, leukocytosis was found with a prevalence of 14% and correlated with active myopathy and/or advanced visceral involvement (73).

Lymphocytosis

Lymphocytosis (lymphocyte count >3,000/mm^3) is a rare hematologic manifestation of SLE and pSS (1%) (55).

Large granular lymphocytosis is an uncommon condition occasionally observed in pSS (229), while in FS patients it has been reported with a frequency of 19% (230). This subset of FS patients presents an elevated number of peripheral and BM large granular lymphocytes (LGL) (230), whose expansion may be reactive or become clonal, giving rise to LGL leukemia. For this reason, it has been suggested that FS and LGL leukemia might represent different clinical aspects of the same disease spectrum (103).

Monocytosis

The percentage of circulating monocytes in SLE patients is usually greater than in normal controls, but an absolute monocytosis (monocyte count >800/mm^3) is unusual; in the setting of RA, monocytosis was reported in patients with synovial effusions (231).

Monocytosis has been documented in 3% of a large cohort of pSS patients (55).

Eosinophilia

Eosinophilia (eosinophil count >500/mm^3) is commonly associated with parasitic infections, atopy or allergic reactions, and may occur in rheumatic diseases, including Churg-Strauss syndrome, eosinophilic myopaties, or eosinophilic fasciitis, as well as ACTDs (232).

In RA patients, eosinophilia is positively related to extra-articular manifestations. Indeed, pulmonary involvement and vasculitis with associated neuropathy and cutaneous ulcerations were 3 times more frequent in eosinophilic patients, and intermittent eosinophilia was found to parallel exacerbations of extra-articular disease (233, 234).

Eosinophilia is an infrequent hematologic manifestation of SLE (235, 236).

In a large series of pSS patients, eosinophilia was detected in 12% of cases (55); patients with eosinophilia presented a lower prevalence of cutaneous vasculitis and positive salivary gland biopsy in the univariate analysis, although only positive salivary biopsy was a significant independent variable in the multivariate analysis (55).

In a cohort of 715 SSc patients, eosinophilia (defined as eosinophil count >400/mm^3) had a prevalence of 7% (237).

Thrombocytosis

Thrombocytosis (platelet count >400,000/mm^3) may represent the expression of a myeloproliferative disorder, or a reactive process in the setting of infections, malignancies, acute bleeding, major surgery tissue damage, drug reactions, or chronic inflammatory conditions, such as ACTDs (238).

Thrombocytosis in ACTDs may depend on BM response to TPO, which acts as acute phase protein, and other cooperating factors, such as interleukin (IL)-6 (239).

Thrombocytosis is a frequent manifestation of RA, correlating with the disease activity (240, 241).

In a series of 465 SLE patients, thrombocytosis was reported with a prevalence of 3.65% (242). Besides constituting an expression of active disease, the sudden appearance and persistence of thrombocytosis or even the apparent reversal of thrombocytopenia in SLE patients was suggested to be indicative of autosplenectomy, particularly in the presence of aPL or sAPS (242).

In SSc patients, thrombocytosis was reported as a disease activity index (73, 243).

Castleman's lymphadenopathy

Castleman's disease or angiofollicular lymphoid hyperplasia is a rare clinicopathologic entity belonging to atypical

LPDs, a heterogeneous group of conditions characterized by lymphoid proliferation not clearly recognizable as either purely reactive or fully neoplastic in nature (244). Three histological (hyaline vascular, plasma cell, and mixed type), and two clinical (localized and multicentric) variants of Castleman's disease have been described. Besides lymphadenopaties, patients frequently show constitutional symptoms and laboratory abnormalities, such as anemia, hypoalbuminemia, hypergammaglobulinemia, and increased acute-phase proteins (244). Dysregulated overproduction of IL-6 is implicated in the disease pathogenesis, and the blockade of the IL-6 signal may be effective in treating patients unresponsive to glucocorticoid therapy (245).

Interestingly, CD is estimated to occur in 11%-30% of patients affected by POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes) syndrome (246), in which, besides IL-6, cytokines such as IL-1β, IL-2 and tumor necrosis factor-α (TNF-α) are involved (247), sharing common immunopathologic pathways with ACTDs.

Histologic features of Castleman's disease have been described in ACTDs, such as SLE (248, 249), pSS (250, 251), MCTD (252), RA (253), and RP (254).

Hematologic malignancies

Large population-based and case control studies evidenced that autoimmune disorders are associated with an increased risk of hematologic malignancies (255-260), likely due to chronic systemic immune stimulation, and/or genetic/environmental shared factors (259). Moreover, pharmacologic treatments of ACTD might contribute to enhance oncogenic risk, either by direct mutagenesis or by interferences with immune surveillance and/or immunocompetent cell proliferation.

A recent meta-analysis of the available cohort studies (6 studies for SLE, 8,700 patients; 9 studies for RA, 95,104 patients; 5 studies for pSS, 1,300 patients) assessing the link between the development of non-Hodgkin's lymphoma (NHL) and ACTDs has provided evidence that NHLs are more common in these patients than in general population, with the highest risk for pSS [standardized incidence rate (SIR) = 18.8], moderate for SLE (SIR = 7.4), and lower risk for RA patients (SIR = 3.9) (Table V) (261).

In most cases, ACTD development was found to precede the onset of lymphoma (261).

Positive associations are most evident for specific NHL subtypes. Diffuse large B-cell lymphoma is primarily increased in RA, SLE, and, to a lesser extent, in SS; lymphoplasmocytic type is often associated with RA, and marginal zone lymphoma (MZL), a low-grade (indolent) B-cell lesion, is strongly associated with SS (Table V). T-cell NHLs are uncommonly found in ACTD patients (119, 260, 262-264).

In RA, consistent with the concept that chronic inflammation associated with ongoing-B-cell proliferation may favor B-cell oncogenic events (262), severe inflammatory activity, high functional class, advanced age, and longstanding disease have been identified as major risk determinants for the NHL development (255, 262, 265) (Table V).

The notion that LPD risk might be associated with medications (and in particular with TNF-α antagonists) is still debated (255-257, 260, 262, 265, 266). In a population based-study on a cohort of 74,651 RA patients, treatment with disease-modifying antirheumatic drugs including methotrexate (MTX) was not found to be a risk factor for malignant lymphomas, and did not further increase the elevated risk in patients with high disease activity (265). Moreover, it has been suggested that effective therapies, by reducing disease activity, might eventually reduce the LPD rates (265).

In a pooled cohort study including 1,152 TNF-α antagonist users, and 7,306 MTX users, biologic agents did not confer a substantial increase in the risk of hematological malignancies compared with MTX (266).

SLE patients developing NHLs usually show aggressive disease (263) (Table V), however, nephropathy and the use of immunosuppressive agents do not appear to confer enhanced risk (264). The increased LPD risk is observed even early in SLE course (and thus unlikely related to cumulative treatments), further suggesting that drug exposure is not the main cause of lymphomagenesis (263).

pSS patients exhibit a 28-fold higher risk of developing MZL than the general population (260), so that SS has been considered a crossroad between autoimmune disorders and LPDs (119). In pSS patients, clinical and biological predictors of NHL development appear to be splenomegaly, lymphoadenopaties, cutaneous vasculitis, peripheral neuropathy, anemia, lymphopenia, as well as parotid enlargement, $CD4^+$ T

Table V. Non-Hodgkin's lymphoma (NHL) in autoimmune connective tissue diseases (ACTDs) (119, 260-265, 274).

ACTD	Risk	ACTD-related risk factors SIR	Prevalent histologic NHL subtypes
RA	3.9	inflammatory activity	diffuse large B cell lympho-plasmocytic
SLE	7.4	inflammatory activity	diffuse large B cell
SS	18.8	skin vasculitis, peripheral neuropathy, anemia, parotid swelling, splenomegaly, lymphadenopaties, lymphopenia, $CD4^+$ T lymphocytopenia, hypocomplementemia, monoclonal mixed cryoglobulinemia, negativization of previously + rheumatoid factor	marginal zone
DM	3.6	–	–
PM	3.7	–	–

SIR: standardized incidence rate; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; DM: dermatomyositis; PM: polymyositis.

lymphocytopenia, monoclonal mixed cryoglobulinemia, hypocomplementemia, and the negativization of a previously positive RF (119) (Table V). The suggested predictive value of abnormal serum immunoglobulin free light chain (FLC) κ:λ *ratio*, that has been found to correlate with disease activity in pSS, RA, and SLE, deserves further investigation (267).

Statistically significant increased risk of Hodgkin's disease (HD) was observed in patients with RA (odds ratios = 2.7) (259). Consistent excesses of HD were found in both sexes, and in early and late RA course (268).

In SLE patients, an increased risk of HD was documented by a recent review of the literature, yielding a SIR of 3.16 (269). Otherwise, in pSS patients HD has been rarely described (119).

In SSc patients, a significant increase in hematologic malignancy risk (SIR = 2.3) was reported in a population-based retrospective study (270), but this finding was not further confirmed (271-273).

Both DM and PM were found to be significantly associated with NHLs (SIR = 3.6 and 3.7, respectively) (274) (Table V). In PM patients, an elevated risk for HD was also described (275). The excess risk was highest at the time of diagnosis, remaining relevant throughout the disease course (274-276).

NHL and HD have been occasionally documented in RP (277, 278) and pAPS (122, 279) patients.

A consistently increased risk for leukemias was evidenced in RA patients (256), with an estimated SIR of 2.47 (280). Chronic myeloid leukemia has occasionally been reported in SLE (281), and SSc patients (282, 283).

A higher incidence of monoclonal serum proteins, mainly κ or λ FLCs, was found in pSS patients compared to those with other ACTDs, such as SLE, RA and SSc, suggesting the coexistence of a B-cell monoclonal process with the polyclonal B-cell expansion characteristic of the disease (119).

The occurrence of multiple myeloma has been observed in pSS (119, 284-286), SLE (287-290), RA (17, 256), and occasionally in SSc (282), DM (291) or RP (292) patients.

Conclusions

The production of blood cells is under the control of self-renewing hematopoietic stem cells whose proliferation and differentiation is dictated by microenvironmental factors, including cell-to-cell stromal and homotypic interaction, as well as by cytokines. Hematopoietic cytokine signal may act in a stimulatory or inhibitory fashion directly on hematopoietic cell function or on their progeny release from BM to the circulation. Colony-stimulating factors support the production of blood cells, whereas many pro-inflammatory cytokines may suppress hematopoiesis (293).

In this regard, cytokine-mediated processes, such as diversion of the iron traffic, decreased iron availability for the erythron, impaired EPO production, and blunted EPO response, ultimately result in the genesis of ACD (4) (Table II).

Besides the effects of the pro-inflammatory network, hemopoietic failure in ACTDs may directly depend on autoimmune humoral and cellular mechanisms, which may also affect peripheral blood cell turnover, survival and functions.

Therefore, autoimmunity/inflammation-related mechanisms may contribute to the high frequency of hematologic quantitative disorders in ACTDs.

Reflecting the effects of the autoimmune/inflammatory action on hemopoiesis, hematologic abnormalities also represent important ACTD prognostic factors. Thus, hematologic surveillance of ACTDs patients may be a reliable and simple method to monitor disease activity and outcome.

On the other hand, careful hematologic controls are required by most of the ACTD pharmacologic therapies, including biologic agents, as suggested by recent reports on quantitative disorders of one or more blood cell lineages in patients treated with this drug class (294-296).

Furthermore, ACTD patients display a consistently enhanced risk of hematologic malignancies, mainly LPDs, primarily represented by B-cell NHLs. The highest NHL risk has been observed in pSS, moderate in SLE, and lower in RA and DM/PM patients. The severity of chronic inflammation emerged as the main ACTD-related risk factor for LPD development.

Interestingly, the predominant histologic variant among NHLs associated with RA and SLE patients is diffuse large B-cell lymphoma, a relatively aggressive type, whereas in SS patients the prevalent subtype is MZL, a low-grade (indolent) B-cell lymphoma closely related to mucosa-associated lymphoid tissue.

NHL subtypes develop at different stages/pathways of lymphoid differentiation, thus, identical pathobiologic processes unlikely occur in LPD development among patients with different ACTDs. However, (antigen-driven?) proliferative stimuli may constitute the link between chronic immune activation/dysregulation and malignant transformation, creating an increased risk for genetic aberrations that may lead to uncontrolled clonal proliferation. Moreover, in the setting of autoimmunity/inflammation, some pro-inflammatory cytokines might further function as autocrine growth factor for aberrant lymphoid cells, amplifying their growth and survival (293).

Revealing the nature of lymphomagenesis in relation to autoimmunity/inflammation will allow to identify subjects at risk and to plan the appropriate diagnostic and therapeutic options.

Moreover, ACTD treatments have been suggested to play a role in lymphomagenesis, however, little support to this hypothesis has been presently provided by the published studies.

Further observations will allow to verify this potential and to elucidate the relative contributions of immune activation and immunosuppression.

In conclusion, a particularly careful hematologic surveillance is needed in patients suffering from ACTDs, due to the high frequency of hematological manifestations, including the consistent risk of hematologic malignancy.

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