Best Practice & Research Clinical Rheumatology 33 (2019) 101425

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

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Suspected systemic rheumatic diseases in patients presenting with cytopenias

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Keywords:
Anemia
Leukopenia
Lymphopenia
Neutropenia
Thrombocytopenia
Bone marrow
Autoimmune disease
Lupus
Immunological tests
Antiphospholipid antibodies

A B S T R A C T

Cytopenias may herald or concur with the onset of various systemic rheumatic diseases. Accordingly, patients with reduced blood cell counts are often referred for possible underlying autoimmune disease. Initial evaluation aims to exclude nonrheumatic causes such as drug toxicity, infections, or hematological/myelopoiesis disorders. Patient interview and physical examination are critical to unravel features related to or suggestive of rheumatic disease. Based on the clinical scenario, targeted immunological testing may provide additional diagnostic insights. Yet, not all patients may present with full-fledged, criteria-classified disease at early stages. Accordingly, physicians should have a high index of suspicion for individuals who present with a combination of immune/inflammatory cytopenia(s) and relevant clinical (e.g., synovitis) and/or serological manifestations, even if these are few in number or nonspecific (e.g., ANA). Ongoing studies in preclinical or early autoimmunity cohorts could lead to the discovery of diagnostic biomarkers applicable also to patients with cytopenias and suspected rheumatic disease.

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https://doi.org/10.1016/j.berh.2019.06.007
1521-6942/

Introduction

Peripheral blood cells, the circulating cellular components of the blood consisting of white blood cells (leukocytes), red blood cells (erythrocytes), and platelets, are both «*offenders*» and «*victims*» in systemic autoimmune diseases. Thus, in several of these disorders, blood cells may be reduced (cytopenia) as a result of direct cell targeting by autoantibodies or activated immune cells, and dysmyelopoiesis, the latter reflecting deregulated function of bone marrow (BM) progenitor and stromal cells. Notably, it has long been appreciated that peripheral blood cell abnormalities, especially cytopenias, may precede the onset or concur with the clinical onset of autoimmune disorders such as systemic lupus erythematosus (SLE) [1]. In this context, identification of immune-mediated cytopenias (i.e., following exclusion of other causes) can be particularly helpful to establish or rule in the diagnosis of a systemic rheumatic disease. In this review, we define and discuss the prevalence of cytopenias in systemic rheumatic diseases. We provide guidance regarding their evaluation in routine clinical practice, as well as their consideration in the diagnostic workup on autoimmune diseases such as SLE. Finally, we highlight the major differential diagnosis to be considered.

Definition and grading of peripheral blood cell cytopenias

The term *isolated cytopenia* is used when a single blood cell type is affected, while *pancytopenia* refers to synchronous depression of all three cell lines. The term *bicytopenia* (i.e., decreases in two cell lineages) is rarely used in clinical practice, as the list of potential causes and investigation is the same with pancytopenia [2]. Isolated cytopenia of any lineage represents a wide spectrum of differential diagnosis, whereas evaluation of pancytopenia is more restricted, yet imperative, to exclude potentially severe underlying disorder.

Leukopenia

Leukopenia typically refers to a decrease in circulating white blood cells (WBCs) below 4.4×10^9 cells/L. As neutrophils and lymphocytes are the most abundant WBCs in peripheral blood, leukopenia may occur in the setting of lymphopenia, neutropenia, or both. *Lymphopenia* is characterized by abnormally low levels of lymphocytes; however, lymphocyte count above 1×10^9 cells/L is not considered clinically significant and should not elicit further investigation unless symptoms are present [3]. *Neutropenia* is generally defined as absolute neutrophil count (ANC) below 1.5×10^9 cells/L; the World Health Organization (WHO) has set a different threshold of 1.8×10^9 cells/L [4]. The terms leukopenia and neutropenia are often used interchangeably mainly because ANC is the determining factor for the increased risk of infection encountered in patients with leukopenia. Severity of neutropenia is categorized as mild (ANC 1000–1500 cells/μL), moderate (ANC 500–1000 cells/μL), and severe (ANC below 500 cells/μL). Agranulocytosis is used for ANC less than 200 cells/μL.

Anemia

Anemia can be defined as a reduction to lower than normal in any of the major red blood cell (RBC) measurements of the complete blood count (CBC) including the absolute RBC count, hemoglobin (Hb) concentration, or hematocrit (Ht) value [5]. The lower normal limit of RBC measurements differs according to gender, age group, race, and specific conditions (for instance, pregnancy, exercising, or smoking). Grading of anemia is essential both for its management and for its differential diagnosis. To this end, two international systems are available, namely, the WHO criteria and the U.S. National Cancer Institute (NCI) grading systems. Although the latter is commonly used, it has been mainly proposed for cancer-related anemia. According to the WHO, anemia is categorized as *mild* (Hb 11–12.9 g/dL), *moderate* (8–10.9 g/dL), and *severe* (<8 g/dL) for males and *mild* (10–10.9 g/dL), *moderate* (7–9.9 g/dL), and *severe* (<7 g/dL) for females.

Thrombocytopenia

Thrombocytopenia is a decrease in platelet count below 150×10^9 cells/L. When in the range of $100–150 \times 10^9$ cells/L, thrombocytopenia is considered mild. *Moderate* thrombocytopenia is defined as a platelet count between 50 and 100×10^9 cells/L and *severe* if platelets are less than 50×10^9 cells/L. Nonetheless, the risk of major spontaneous bleeding becomes substantial when platelet levels drop below 20 to 30×10^9 cells/L, especially when less than 10×10^9 cells/L [6].

Prevalence of cytopenias in systemic rheumatic diseases

Systemic lupus erythematosus (SLE)

Patients with SLE can develop cytopenias due to the disease itself (for instance, thrombotic thrombocytopenic purpura-like) or secondary causes (drug toxicities) (Table 1). Immune-mediated cytopenias including thrombocytopenia, autoimmune hemolytic anemia (AIHA), and leukopenia, especially lymphopenia, are considered a hallmark of SLE and represent frequent criteria-defined manifestations [7]. Notably, cytopenias tend to cluster within the same individuals [8–11] and are strongly associated with antiphospholipid antibodies (aPL) [9,12,13], suggesting a possible common underlying pathogenic mechanism. Cumulative incidence of lupus cytopenias has been estimated to be as high as 90% [7,14,15]. In a large SLE cohort (n = 1437 patients) followed up for an average 4.4 years, 66% developed at least one hematologic manifestation [16].

Leukopenia is the most typical hematologic manifestation and may be the result of neutropenia, lymphopenia, or the combination of both. At the time of SLE diagnosis, leukopenia is found in 5.1%–29.5% of patients [1,14,17], whereas its cumulative incidence is in the range of 42.3–56% [14,15]. As isolated lymphopenia does not always result in leukopenia, it is a more frequent laboratory finding than leukopenia. Thus, lymphopenia is present in 6.3–64.9% of lupus subjects at the time of diagnosis [17–19], increased to 81.9% during long-term follow-up. SLE lymphopenia correlates with higher disease activity [19].

On the other hand, neutropenia is usually mild; therefore, when a patient with SLE presents with moderate to severe neutropenia, secondary causes should be considered (e.g., drug toxicity, malignancies) [20]. Observational data suggest that neutropenia may be the initial manifestation in approximately 25% of patients, while its overall prevalence approximates 47% [18].

Thrombocytopenia represents the second most frequent type of immune-mediated cytopenia in SLE. At the time of diagnosis, it is encountered in 5.2% [14] to 20% [1,9,19] of patients, with an overall prevalence of 20–30% [14,15,18]. Nonetheless, only 25% of individuals with SLE thrombocytopenia

Table 1
Causes of cytopenia in patients with systemic lupus erythematosus (SLE).

Anemia	Thrombocytopenia	Lymphopenia	Neutropenia
Anemia of chronic disease	Immune-mediated	Immune-mediated	Immune-mediated
AIHA	Drug-induced (e.g., CYC)	Drug-induced (Glucocorticoids)	Drug-induced (e.g., CYC and AZA)
Nutritional deficiencies (iron, folate, B12)	Infections (particularly viral)	Infections, particularly viral	Infections
Drug-induced	HLH		Hematologic malignancies
DIC, TTP-like, HLH	TTP-like, atypical HUS		Myelodysplasia
Hypersplenism	DIC		HLH
Infection	Hematologic malignancies		Aplastic anemia
Myelodysplasia	Hypersplenism		
Aplastic anemia	Myelodysplasia		
Blood loss (e.g., GI blood loss)	Aplastic anemia		

AIHA; Autoimmune hemolytic anemia, DIC; Disseminated intravascular coagulation, TTP; thrombotic thrombocytopenic purpura, GI; Gastrointestinal, CYC; Cyclophosphamide, AZA; Azathioprine, HLH; Hemophagocytic lymphohistiocytosis, HUS; Hemolytic-uremic syndrome.

manifest life-threatening disease (platelet count less than 30×10^9 cells/L), most cases occurring during the course of the disease [9,14].

AIHA is a less common manifestation of SLE and typically (up to 83% of cases) manifests at disease-onset [8,13,18]. Cumulative incidence has been estimated to be 6–11.8% in various cohorts [8,10,14], with the initial disease manifestation in 2.4–8.6% of patients [1,8,14,17]. Pancytopenia is infrequent in SLE (5–10%) and should induce investigation to exclude myelotoxicity or other BM failure syndromes. It can also develop in the life-threatening situation of macrophage-activating syndrome (MAS), which might accompany active SLE – especially in pediatric cases – along with high serum levels of ferritin, triglycerides, and liver enzymes.

Sjögren's syndrome (SS)

Sjögren's syndrome (SS) is characterized by lymphocytic infiltration of exocrine organs and presents with a broad clinical spectrum extending from dryness of the main mucosal surfaces to systemic involvement (extraglandular manifestations) and can be complicated by the development of lymphoma. SS can occur alone (*primary* SS) or in association with other autoimmune diseases (*secondary* SS). Hematological manifestations are seen in primary SS, including anemia, with reported prevalence of up to 34.1% [21,22]. Mild normocytic anemia of chronic inflammation is the most common type encountered, while clinically significant anemia is rare. AIHA has been rarely described (<1%) [23] and correlates with thrombocytopenia, leukopenia, hypocomplementemia, and primary biliary cirrhosis (PBC) [22,24].

Leukopenia is noted in as many as 15% patients with primary SS. On the other hand, severe neutropenia, although documented in a number of published cases [25], is relatively uncommon and should alert the physicians for excluding underlying lymphoma. Possible mechanisms for the occurrence of neutropenia in pSS have implicated both the existence of antineutrophil antibodies and the immune-mediated inhibition of neutrophil production.

Immune thrombocytopenia has also been described [26] and occurs in 5–15% of patients with SS. Notably, SS has been reported to be the second most frequently associated autoimmune disease (following SLE) [27], suggesting that it should always be considered in patients presenting with immune thrombocytopenia. On the other hand, thrombotic thrombocytopenic purpura (TTP), a potentially lethal multisystem disorder, is extremely rare [28].

Rheumatoid arthritis

Rheumatoid arthritis (RA) *per se* is generally not characterized by immune-mediated cytopenias. Accordingly, when cytopenias develop in the context of RA, they are usually attributed to comorbidities or drug toxicity. Notwithstanding, Felty's syndrome (FS) represents a rare extra-articular manifestation characterized by neutropenia with ANC below 2000 cells/μL and splenomegaly [29]. It typically manifests in seropositive patients with longstanding (exceeding 10 years) and active disease, while it is extremely rare in early disease, suggesting an underlying role of persistent inflammation and immune activation. The lifetime incidence of FS has been estimated to approximately 1% [30]. However, its true prevalence tends to decrease over the years probably due to better control of arthritis. Patients with FS may also have thrombocytopenia due to hypersplenism or anemia of chronic disease.

Other rheumatic diseases

Systemic sclerosis (SSc)

Thrombocytopenia and microangiopathic hemolytic anemia (MAHA) can be seen in the context of *scleroderma* renal crisis (SRC), which represents one of the most feared complications occurring in approximately 10% of patients with systemic sclerosis (SSc) [31]. It manifests with sudden onset of high blood pressure and kidney failure, especially in patients with rapidly progressive diffuse cutaneous involvement and serum anti-RNA polymerase III antibody. It may be also accompanied by headache, visual disturbance, seizures, congestive heart failure, and pericardial effusion and requires aggressive treatment with ACE inhibitors [32].

Mixed connective tissue disease (MCTD)

MCTD combines features of SSc, SLE, polymyositis, and RA and is characterized by the presence of anti-U1 RNP antibodies and the absence of severe renal and CNS involvement. Leukopenia, particularly lymphopenia, is observed in the majority (>60%) of patients, while thrombocytopenia is uncommon [33].

Antiphospholipid syndrome (APS)

Thrombocytopenia is included among the "non-criteria" manifestations observed in 20–50% of patients with primary *antiphospholipid syndrome* (APS) [34]. Although usually mild and not requiring clinical intervention, it has been associated with the occurrence of APS-related events, namely, vascular thrombosis and miscarriages. More severe forms of thrombocytopenia can be observed in the context of underlying connective tissue disease (mainly SLE) or catastrophic APS (CAPS), a rare yet potentially fatal form of APS. In CAPS, widespread intravascular thrombosis results in multiorgan failure, especially when MAHA is present (1/3 of cases) [35].

Adult-onset Still's disease (AOSD)

AOSD is a systemic autoinflammatory disease where increased neutrophil count (neutrophilia) is observed (>80%). The majority of patients manifest normocytic, normochromic anemia of chronic disease and reactive thrombocytosis, especially during active disease [36,37]. On the other hand, pancytopenia – along with high serum levels of ferritin, triglycerides, and liver enzymes – is observed in the life-threatening situation of MAS, which can complicate 12–14% of cases with AOSD (*discussed below*) [38].

Sarcoidosis

Sarcoidosis is a systemic inflammatory disease characterized by the formation of non-caseating granulomas in one or multiple organs. Lymphopenia is a typical laboratory finding occurring in more than 50% of cases and has been associated with chronic disease [39]. Interestingly, significant lymphopenia (less than 1.0×10^9 cells/L) has been linked to underlying sarcoidosis in patients presenting with uveitis [40]. Thrombocytopenia in sarcoidosis can stem from three main mechanisms: platelet sequestration and destruction in the spleen, BM granulomatous infiltration, and autoimmune destruction, the latter mechanism accounting for more than 80% of cases [41]. Notably, immune-mediated thrombocytopenia in sarcoidosis can be particularly severe, often complicated by bleeding diathesis but usually has a favorable response to therapy [41].

Investigation for possible systemic rheumatic disease in patients with cytopenias (Fig. 1)

Patient history

In patients presenting with cytopenia(s), a comprehensive medical history is important to rule in the possibility of an underlying autoimmune disease. Relevant drug exposure, symptoms suggestive of viral illness, and recent travel history should always be documented. Next, it is vital to elicit any history of low-specificity constitutional (e.g., fatigue, fever) or clinical symptoms (e.g., photosensitivity, arthralgias, morning stiffness, myalgias, or Raynaud's) or other features that are common in the general population (e.g., hair loss, sicca), which, nevertheless, when accumulated, should raise the clinical suspicion for an underlying rheumatic disease. Emphasis should be put on the obstetric history of a female patient, particularly for APS-related morbidities (e.g., recurrent pregnancy loss, fetal death, pre-eclampsia) [42]. Physicians should be aware that patients with pre-existing autoimmune disease (for instance, Hashimoto thyroiditis) are at risk for developing another autoimmune disorder [43]. Furthermore, family history for autoimmune conditions should be considered as an additional risk factor [44]. Finally, the pattern of cytopenias can be helpful in guiding the cause, as a relapsing-remitting presentation is more consistent with an autoimmune process rather than infections, hematological diseases, drug toxicity, or malignancies.

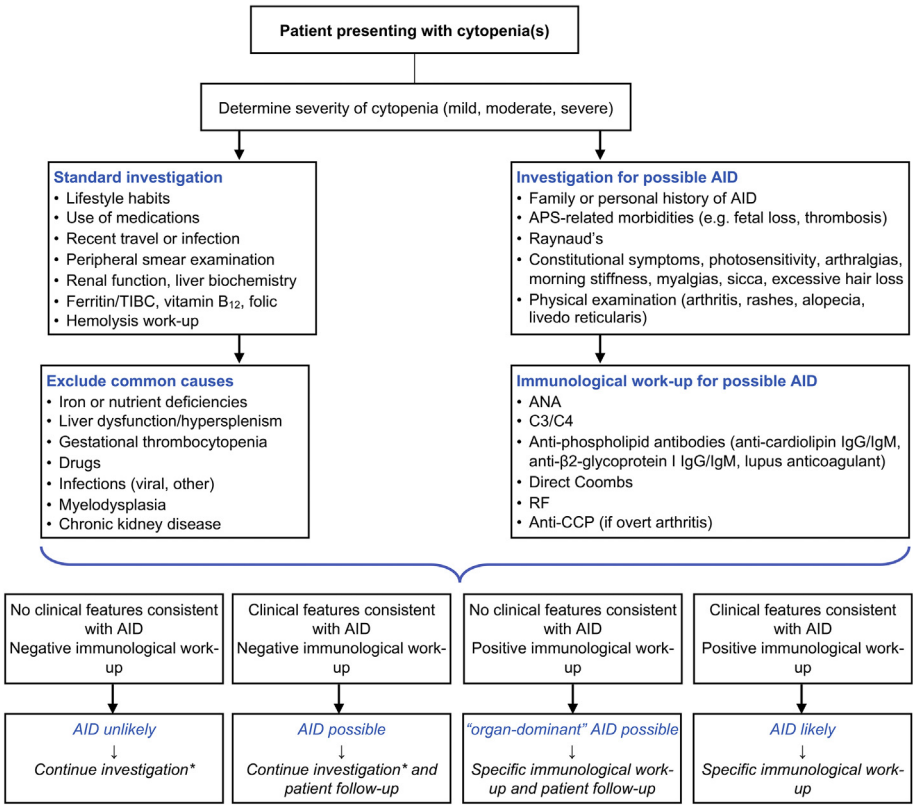

Fig. 1. Diagnostic approach to the patient with cytopenia(s) and suspected autoimmune disease (AID). TIBC, total iron-binding capacity; APS, antiphospholipid syndrome. * Consider bone marrow examination.

Physical examination

The primary goal of physical examination is to detect clinical findings that cannot be tracked by medical history. The physician should have a low threshold to detect signs such as skin rashes (e.g., facial or trunk erythema, polycyclic rashes), livedo reticularis, digital or mucosal (oral or nasal) ulcers, objective hair loss, or arthritis. Their presence, especially in combination, may suggest the presence of a connective tissue disease as the cause of the investigated cytopenia. In particular, all patients presenting with cytopenias should be meticulously examined for synovial edema or other signs suggestive of arthritis, which represents the most frequent clinical feature in autoimmune rheumatic diseases.

Immunological workup

Although the diagnosis of rheumatic diseases is largely clinical, immunological testing may be particularly useful. In general, antinuclear antibodies (ANA) are performed in any patient with suspected autoimmune disease, while more specific autoantibodies are looked for depending on clinical suspicion. The recommended method of ANA testing is by indirect immunofluorescence using Hep2 or Hep2000 as a substrate [45]. Nevertheless, physicians should be aware that the specificity of ANA is not high for any rheumatic disease [46], while a proportion of patients with autoimmune disease will not have autoantibodies, especially at early stages. For instance, approximately 10–15% of patients with SLE may have negative or low-titer ANA at the time of clinical diagnosis [47]. In our experience, a

proportion of these patients may exhibit low serum concentrations of C3 or C4; therefore, testing for these markers can be helpful to rule in the possibility of SLE [48]. If there is moderate or high suspicion for SLE, anti-dsDNA, C3/C4 levels, and ENA (extractable nuclear antigens) screening (including anti-SSA/Ro, anti-SSB/La, anti-RNP, and anti-Sm) should be ordered.

aPL, including anti-cardiolipin IgG/IgM, anti-β2-glycoprotein I IgG/IgM, and lupus anticoagulant, should be tested if there is suspicion for underlying APS or in the context of unexplained thrombocytopenia and hemolytic anemia [12]. In such cases, positive aPL often coexists with hypocomplementemia. Positive direct Coombs in the absence of frank hemolysis should also raise the suspicion for lupus [49].

Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) are seen mainly in patients with rheumatoid arthritis, but RF can be positive in numerous other chronic inflammatory conditions. For example, some patients with SS have positive RF and low complement C4, especially in the setting of cryoglobulinemia, or vasculitic disease or associated lymphoma [50]. Other autoantibodies should not be ordered unless there is specific clinical syndrome and indication (for example, myositis-specific antibodies). Inflammatory markers (i.e., C-reactive protein, erythrocyte sedimentation rate) are rarely helpful in evaluating the cause of cytopenia.

Blood smear examination

The importance of peripheral blood film examination in the evaluation of cytopenia(s) cannot be overemphasized. A detailed description of possible findings and their differential diagnosis falls outside the scope of this review [51]. Notably, blood smear examination is essential in cases of thrombocytopenia to exclude artifactual reduction and unravel signs of peripheral platelet destruction (i.e., increased number of large/giant platelets) suggestive of an immune-mediated process. In the context, identification of red blood cell schistocytes may alert physicians for the diagnosis of TTP. Examination of white blood cells may help to diagnose lymphoproliferative disorders.

Bone marrow examination

BM aspiration/biopsy should be considered if the initial (noninvasive) workup fails to confirm the diagnosis or the response to treatment is inadequate. The decision to perform biopsy is directed by the severity of cytopenia(s), peripheral blood smear abnormalities, and the presence of complications due to cytopenia(s), especially when primary hematologic disease or BM failure syndromes are suspected [52] (Table 2). In the setting of drug toxicity, BM findings are often unremarkable, although granulocytic maturation arrest at the myelocyte stage and an increase in eosinophils and dyserythropoiesis can be seen [52,53].

In immune-related cytopenias, BM findings may not always be diagnostic. For example, in peripheral platelet destruction (immune thrombocytopenia), BM evaluation may reveal increased numbers of megakaryocytes or be completely normal [54]. In patients with SLE, BM findings can be variable according to the prevailing mechanism implicated in the pathogenesis of cytopenias [55]. Thus, pancytopenia is often accompanied by BM hypoplasia and dyserythropoiesis, although lymphocytosis and plasmacytosis may also be present. In case of peripheral blood cell destruction such

Table 2
Indications for performing bone marrow aspiration and biopsy.

Unexplained anemia, leukopenia, thrombocytopenia
Pancytopenia
Abnormal findings on peripheral smear (blasts, teardrop red cells, and hairy cells)
Suspected multiple myeloma
Staging of non-Hodgkin's lymphoma
Unexplained splenomegaly
Suspected deposition or storage disease (amyloidosis, Niemann–Pick disease, and Gaucher disease)
Fever of unknown origin (FUO) in immunocompromised patients
Confirmation of normal bone marrow in potential allogeneic donor

as in lupus thrombocytopenia, hyperplastic BM may be detected [55–57], with global hypocellularity, increased reticulin proliferation, and necrosis. Nevertheless, a variety of other pathologic findings can be detected including megakaryocytic atypias, dyserythropoiesis, hypocellularity, BM necrosis, and disruption of the BM architecture, characterized by abnormal localization of immature precursors [57]. Of note, similar myelodysplasia-like findings can be found in the BM of patients with RA as well as patients with other autoimmune or inflammatory diseases, suggesting that these abnormalities are due to chronic inflammation [57]. Granulocytic hypoplasia was observed in 47.3% (9/19) of SLE individuals with leukopenia. Myelofibrosis and aplastic anemia have been rarely reported as causes of pancytopenia in SLE [58,59].

Classification criteria: useful as a guide but not diagnostic

Classification criteria have been mainly developed to recruit patients with certain diagnoses for clinical studies but are also commonly used in clinical practice to aid in the diagnosis of rheumatologic diseases [48,60]. At initial presentation, not all patients will fulfill the corresponding criteria, indicating that clinical diagnosis may precede classification.

Systemic lupus erythematosus

In the case of SLE, two sets of classification criteria are available [49,61], while new criteria have been recently announced jointly by the EULAR and the ACR [62]. Cytopenias are included in all three sets of criteria, although there are important differences in terms of their definition and weight. Notably, lymphopenia *per se* is included in the ACR and SLICC criteria, whereas the EULAR/ACR criteria account only for leukopenia. The prerequisite for one or at least two measurements is also different. Furthermore, the revised ACR 1997 criteria [61] have merged all cytopenias (hemolytic anemia, lymphopenia, leukopenia, and thrombocytopenia) into a *single* criterion. In the 2012 SLICC criteria [49], cytopenias are represented in three distinct criteria, one for each of hemolytic anemia, leukopenia/lymphopenia, and thrombocytopenia. Consequently, the SLICC criteria enable earlier identification of patients with SLE along with predominant hematologic disease [63], although this might also carry a risk for false-positive diagnoses. To avoid "over-representation" of the hematology domain in SLE classification, the new EULAR/ACR criteria weighs leukopenia with a score of 3, whereas thrombocytopenia and hemolytic anemia are scored with 4; patients with bi- or pancytopenia will also get a maximum score of 4 (out of 10, which enables SLE classification) [62]. However, a possible drawback of the new criteria is that they consider only leukopenia (white blood cells less than 4000×10^9 cells/L) and not isolated lymphopenia, which might compromise their sensitivity at early disease stages.

A number of comparative studies have demonstrated that the SLICC criteria are more sensitive than the ACR criteria, especially in early disease [64], whereas the new EULAR/ACR criteria have not been extensively tested. Yet, the diagnostic performance of the criteria may be suboptimal at early stages with a proportion of patients falling short of the classification thresholds [60,63]. To this end, ANA positivity, inflammatory arthritis, and cytopenias represent the most frequent presentations among patients with SLE who, at the time of physician-based diagnosis, fulfill only three ACR 1997 criteria [65]. Relevant to this is also the fact that some patients may present with "*organ-dominant*" (in particular, "*hematological-dominant*") disease, thus posing diagnostic and therapeutic challenges [60,66]; the majority will eventually evolve into "*full-blown*" SLE during a period of months to years. In such cases, vigilance is recommended to detect mild serological abnormalities and extra-hematological signs (for example, a case of moderate/severe thrombocytopenia with low C3 and photosensitive rash).

Sjögren's syndrome

The 2016 ACR/EULAR classification criteria [67] for primary SS managed to reach high sensitivity and specificity (96% and 95%, respectively), indicating that it may be a useful tool in clinical practice. According to the authors, these criteria are applicable to patients with symptoms of ocular or oral dryness or suspicion of SS due to the presence of systemic features based on the ESSDAI (European League Against Rheumatism SS Disease Activity Index) [68]. The latter is a systemic disease activity

index, which includes 12 domains, each divided into 3–4 levels of activity. The hematological domain of ESSDAI requires the presence of immune-mediated cytopenia and the exclusion of secondary causes to be attributed to SS activity. The inclusion of the ESSDAI in the criteria allows to classify patients with no sicca symptoms, enabling the earlier classification of the disease and the recognition of patients with predominantly systemic manifestations.

Antiphospholipid syndrome

Contrary to SLE, definitive APS diagnosis is supported by classification criteria [42], according to which, at least one clinical manifestation (thrombotic event or pregnancy complications) and one immunologic criterion (positive test for LA, moderate to high titers of anti-CL and/or anti-β2GP1) must be met [42,69]. Notably, despite the fact that noncriteria manifestations are common and 20–50% of patients with APS develop mild to moderate thrombocytopenia [34], they are not included in the existing APS criteria.

Pertinent differential diagnosis

Hematologic abnormalities, mainly isolated cytopenias, are frequent in clinical practice and require thorough evaluation with regard to the underlying clinical condition. Most common causes include infections and drug toxicity; however, hematologic malignancies and BM failure syndromes should also be considered in certain situations. Oftentimes, these conditions may be accompanied by nonspecific signs and symptoms such as arthralgias, fatigue, low-grade fever, and rashes, which are also seen in systemic autoimmune diseases. Consequently, astute physicians should be aware of the commonalities and differences.

Hematological malignancies

Common malignancies of the lymphatic and hematologic system include leukemias, lymphomas, myeloproliferative neoplasms, and plasma cell dyscrasias. At early stages, they can be completely asymptomatic or present with nonspecific constitutional symptoms. Hematologic malignancies can result both in peripheral blood cytopenias and in hypercytosis. The clinical presentation of leukemia relates to complications due to affected cell lineage(s) and may include fatigue, weakness, pallor skin, infections, ecchymoses, and petechiae. Hepatomegaly/splenomegaly may be present, while lymphadenopathy is rare. Chronic leukemia (e.g., B-cell chronic lymphocytic leukemia) may be asymptomatic, while splenomegaly is common as well as bleeding episodes due to platelet dysfunction [70]. Peripheral smear and BM examination are required in case of suspicion, while further investigation is guided by the BM findings. Systemic complaints including fever (>100.4 °F), weight loss, and night sweats are characteristic. Elevated levels of serum lactate dehydrogenase (LDH) and uric acid are common laboratory findings, while cytopenias develop in case of BM infiltration. Generally, lymphadenopathy due to lymphoma is more extensive than those seen in autoimmune diseases. Multiple myeloma (MM) and related disorders generally present with anemia, while leukopenia or thrombocytopenia is uncommon. Anemia in combination with other features such as renal disease, bone pain, and hypercalcemia should raise suspicion of MM [71].

Drug toxicity

Drugs account for a considerable percentage of cytopenias encountered in clinical practice. The mechanism can be either immune-mediated toxicity or direct BM toxicity. Although isolated cytopenias are most common, pancytopenia can be present in cases of BM toxicity.

Myelosuppression is a common adverse event of cytotoxic drugs, such as alkylating agents and antimetabolites; however, non-neoplastic cells can also be offenders [72]. To this end, immunosuppressives (e.g. azathioprine), non-steroid anti-inflammatory drugs (NSAIDs) (e.g. phenylbutazone) and antibiotics such as chloramphenicol can also repress the production of blood cells. Aplastic anemia has been also associated with anticonvulsants (e.g., felbamate, valproic acid, carbamazepine, and

phenytoin), sulfonamides, and nifedipine [73]. The most common drugs causing isolated anemia due to direct BM insult are antiretroviral medications and other antiviral agents, methotrexate, phenytoin, and hydroxyurea.

Drug-induced immune hemolytic anemia (DIIHA) is a rare condition but should be considered if patients are on potentially responsible medication [74]. Specifically, 42% of drug-induced hemolysis cases are caused by antibiotics, 16% by NSAIDs, and 13% by antineoplastic agents. Cephalosporins are commonly implicated in DIIHA; cefotetan accounts for more than of 50%, while ceftriaxone, piperacillin, and purine nucleoside analogs are also common offenders [74]. Glucose-6-phosphate dehydrogenase (G6PD) deficiency should be considered in patients with hemolytic anemia receiving antimalarial medicines (e.g., quinine), aspirin, sulfa drugs, and antibiotics, particularly quinolones and nitrofurantoin.

Numerous drugs have been reported as potential causes of *leukopenia* and *neutropenia*. Both direct toxicity to BM and immune-mediated destruction of neutrophils have been implicated [75]. Common drugs involved in immune-mediated neutropenia are antithyroids, clozapine, ticlopidine, beta-lactams, trimethoprim-sulfamethoxazole, sulfasalazine, vancomycin, rifampicin, furosemide, spironolactone, IVIG, anti-TNF agents, and rituximab. Neutropenia due to rituximab can occur late rather than early after administration [76]. Lymphopenia *per se* can be caused by glucocorticoids. On the other hand, isolated neutropenia due to BM suppression can be caused by methotrexate, cyclophosphamide, colchicine, azathioprine, and ganciclovir. However, these drugs frequently affect more than one lineage.

Similarly, *drug-induced thrombocytopenia* (DITP) can be caused by either an immune-mediated mechanism or myelotoxicity. It can present as severe, potentially life-threatening thrombocytopenia [77]. Definitively implicated drugs include quinine, quinidine, trimethoprim-sulfamethoxazole, ibuprofen, vancomycin, GP IIb/IIIa inhibitors, rifampin, carbamazepine, ceftriaxone, penicillin, mirtazapine, oxaliplatin, and heparin. Heparin-induced thrombocytopenia is a rare condition associated with thrombosis and typically occurs approximately four days after initiation of heparin [78]. Isolated thrombocytopenia due to myelosuppression can occur due to linezolid, daptomycin, and valproic acid.

Viral infections

Viral infections are common causes of cytopenias, especially in young individuals, although the incriminating virus is not always identified. Mild cytopenias can occur in the setting of any viral infection, but initial differential diagnosis should include EBV, CMV, HIV, hepatitis virus group, and parvovirus B19. Viruses can induce a wide spectrum of hematologic abnormalities including leukopenia (in particular lymphopenia and neutropenia), thrombocytopenia (immune-mediated or due to hypersplenism), hemolytic anemia (rare), and cytopenias due to cytotoxic effect to BM [79]. Although the majority of cases present as isolated cytopenia, a considerable percentage develop bicytopenia (leukopenia and thrombocytopenia) or pancytopenia, especially if BM is affected.

Lymphopenia and/or neutropenia is a common feature of viral infections. HIV, EBV (infectious mononucleosis), viral exanthematous diseases, and hepatitis A should be considered in the differential and, in case of childhood viral infections, RSV, parvovirus, influenza A and B. Mononucleosis syndrome, caused by EBV in up to 90% cases, typically presents with fever, pharyngitis, atypical lymphocytosis, adenopathy, and fatigue and, less commonly, thrombocytopenia and mild neutropenia [80]. CMV infection generally does not induce neutropenia unless patients are immunocompromised or receive ganciclovir. Neutropenia can be seen in HBV and HCV in case of disease complications such as hypersplenism and cirrhosis.

Isolated thrombocytopenia can occur in the setting of CMV, HIV, parvovirus, HCV, EBV, varicella, and other viruses. In general, any virus causing hypersplenism or severe hepatitis can lead to thrombocytopenia due to platelet entrapment and liver failure (decreased thrombopoietin), respectively. Virus-induced AIHA represents a rare complication of hepatitis A and C viruses, HIV, EBV, rubella virus, parvovirus, and varicella virus [81]. Secondary BM suppression due to aplastic anemia has been associated with parvovirus B19 and EBV. Patients infected by parvovirus may present with a febrile

flu–like illness, various skin rashes including malar rash, and inflammatory arthritis and thus can be misdiagnosed as SLE [82].

Hematologic abnormalities represent a frequent feature in (undiagnosed) HIV-positive patients. Lymphopenia is seen in as high as 26% of patients in clinical presentation, while neutropenia may be present in up to 10% of cases. Thrombocytopenia and anemia are less common in early stages. However, prevalence of each cytopenia is increasing over the course of the disease as CD4 counts decrease [83]. Approximately 5% of HIV-positive patients develop bicytopenia or pancytopenia.

Hemophagocytic lymphohistiocytosis (HLH)

HLH is a rare life-threatening syndrome characterized by fever, splenomegaly, bicytopenia or pancytopenia, hypertriglyceridemia, hypofibrinogenemia, and elevated ferritin in combination with the pathologic finding of hemophagocytosis in BM or other tissues [84]. Coexistence of some of these features should raise the clinical suspicion of HLH, and thus, BM biopsy is warranted. Although typical pathology is the hallmark of the disease, it is not mandatory to establish diagnosis. Nevertheless, BM biopsy is important to rule out other mimicking conditions. With regard to underlying causes, infections, mainly viral, are the leading cause of HLH, followed by hematologic malignancies, especially lymphomas. Of the systemic autoimmune/autoinflammatory diseases, SLE – especially pediatric – and adult-onset Still's disease (AOSD) are associated with HLH. Although HLH is manifested in up to 15% of patients with AOSD [38], lupus is the leading rheumatic disease which causes HLH [85] due to its higher prevalence. Conditions such as RA, vasculitis and inflammatory bowel disease have been reported as rare causes of HLH. The term MAS is used instead of HLH when the underlying cause is a rheumatic disease such as SLE, AOSD, or juvenile idiopathic arthritis.

Myelodysplastic and BM failure syndromes

Myelodysplastic syndromes (MDS) comprise a group of malignant hematopoietic stem cell diseases characterized by dysplastic BM and increased risk of transformation to leukemia. Patients with MDS have decreased production of erythrocytes, granulocytes, and platelets along with susceptibility to infections due to functional deficits of blood cells. At presentation, symptoms and signs are nonspecific or may be completely absent. Anemia is the most prevalent cytopenia and may be isolated or in combination with other cytopenias [86]. However, isolated thrombocytopenia or leukopenia can also occur. Physical examination may be normal, while splenomegaly, lymphadenopathy, and hepatomegaly are uncommon. MDS, which is highly prevalent among the elderly population, is the most common cause of BM failure with typical age of disease onset $\geq$65 years [86].

Notably, 10% of patients with MDS develop immune-mediated manifestations during the course of the disease, including inflammatory arthritis, pernicious anemia, polymyalgia rheumatic, and psoriasis [87]. Other inflammatory manifestations such as serositis, Sweet's syndrome, vasculitis, pulmonary infiltrates, skin rashes, and peripheral neuropathies have also been reported [88]. Thus, physicians should be aware of MDS-related autoimmune features, as some patients may present with rheumatic-associated symptoms.

Conclusion

Cytopenias are common laboratory findings in a variety of medical conditions including rheumatic (especially connective tissue) diseases. In spite of their low specificity, their identification and characterization can be particularly helpful in ruling in or establishing the diagnosis of certain autoimmune diseases. Investigation should begin by excluding other causes such as drug effects, viral infections, and hematological disorders, including lymphohematopoietic dysplasias or malignancies in specific cases. If no apparent cause of cytopenia(s) is found or there are indications for chronic inflammation or immune-mediated destruction of blood cells, the possibility for underlying rheumatic condition is increased. Emphasis should be put to elicit a pertinent history or detect even subtle signs suggestive of inflammatory/autoimmune diseases. Targeted immunological testing may provide additional hints or be diagnostic on certain occasions. The reader should bear in mind that at early stages, systemic

autoimmune diseases may be limited to a single (including the hematological) or a few organs, thus falling short of the classification criteria. In this scenario, physicians should not be reluctant to provide their patients with a tentative diagnosis of the most likely rheumatologic disease (e.g., "incomplete lupus", "pre-lupus", or "lupus-like") as a step forward to initiating proper treatment. For the future, we foresee the identification and validation of molecular or protein biomarkers, which could further assist the early diagnosis of such cases.

Summary

Cytopenias are common laboratory manifestations that can sometimes precede or concur with the onset of various systemic rheumatic diseases. Their pathogenesis involves immune-mediated destruction of blood cells and/or chronic inflammation affecting the BM. Evaluation of a patient presenting with cytopenias and possible rheumatic disease should begin by excluding other causes particularly drug toxicity, viral infections, and hematological disorders or malignancy. Emphasis should be put to elicit any pertinent history of symptoms suggestive of autoimmune disorders, family history of autoimmunity, and obstetric history relevant to APS. Comprehensive physical examination is essential for the detection of even mild signs of rheumatism such as skin rashes, synovitis, and alopecia, followed by syndrome-oriented immunological testing. In this context, classification criteria are useful clinical aids but are not meant to be used as diagnostic and may fail to capture some patients with early-onset, organ-limited autoimmune diseases. Consequently, and following exclusion of other mimicking disorders, patients who present with cytopenia(s) in conjunction with relevant immunological and/or clinical features may receive a provisional diagnosis of rheumatologic disease and be regularly monitored for confirmation and prompt initiation of appropriate treatment.

Funding

George Bertsias has received research grant from the Foundation for Research in Rheumatology (FOREUM, 016BertsiasPrecl). This work is also supported by the Pancretan Health Association.

Conflicts of interest statement

The authors declare no competing interests pertaining to this work.

Practice points

- Cytopenias may precede or concur with the onset of autoimmune disorders such as systemic lupus erythematosus (SLE).
- In the context of systemic autoimmune diseases, lymphopenia is more common than neutropenia; an absolute neutrophil count less than 1000 cells/μL should induce investigation to exclude other causes such as drug toxicity and hematological disorders.
- In SLE, cytopenias tend to cluster and correlate with positive antiphospholipid antibodies and/or low serum complement C3/C4.
- Individuals with unexplained thrombocytopenia should be assessed for history and/or clinical features suggestive of antiphospholipid syndrome, followed by appropriate immunological testing.
- In severe clinical presentations with worsening pancytopenia, macrophage-activating syndrome (MAS) should be excluded.
- According to patient history, symptoms, and signs, targeted immunological testing should be ordered
- At early stages, autoimmune rheumatic diseases such as SLE can be limited to only a few or a single organ; thus, strict adherence to the classification criteria may delay disease diagnosis.

Research agenda

- Prospective evaluation of individuals who present with unexplained cytopenias to determine the actual risk for progression into autoimmune rheumatic disease
- Identification of risk factors (demographic, environmental, and others) for autoimmune disease-related cytopenias
- Identification of novel biomarkers (transcriptomic, genetic, and protein) that can distinguish immune-mediated cytopenias versus other causes and for risk stratification with regard to progression into systemic autoimmune disease
- Analysis of the natural history of cytopenias in individuals with early stages of systemic rheumatic diseases

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