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Differential Diagnosis Of Thrombocytopenia In Rheumatoid Arthritis (A Literature Review).

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Abstract*: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease in which, alongside the thrombocytosis typical of active inflammation, a subset of patients develop thrombocytopenia that requires careful differential diagnostic work-up. The prevalence of thrombocytopenia among RA patients is estimated at 3–10% and varies considerably depending on the diagnostic criteria applied and the cohort studied [Bobircă, 2022, p. 2]. The causes of a reduced platelet count in RA are heterogeneous and include drug-induced myelosuppression (methotrexate, leflunomide, sulfasalazine, gold salts), immune thrombocytopenia (including that associated with anti-platelet antibodies), Felty syndrome, secondary antiphospholipid syndrome, thrombotic microangiopathy, myelodysplastic syndrome, and virus-associated and paraneoplastic mechanisms. This review summarizes current understanding of the etiopathogenesis, clinical and laboratory features, and diagnostic algorithms for thrombocytopenia in RA patients, based on an analysis of Russian- and English-language literature published between 1988 and 2025. A systematic, stepwise approach — from assessing the severity of thrombocytopenia and excluding pseudothrombocytopenia to a targeted laboratory and instrumental search for the specific cause — is shown to substantially shorten the time to diagnosis and reduce the risk of iatrogenic complications. A generalized diagnostic algorithm and a comparative table of differential diagnostic features of the main causes of thrombocytopenia in RA are proposed for use in the clinical practice of rheumatologists, hematologists, and general practitioners.*

Keywords: rheumatoid arthritis; thrombocytopenia; differential diagnosis; Felty syndrome; drug-induced cytopenia; immune thrombocytopenia; methotrexate; antiphospholipid syndrome; thrombotic microangiopathy; myelodysplastic syndrome.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory joint disease with a population prevalence of 0.5–1%, characterized by synovial involvement, destruction of cartilage and bone, and a broad spectrum of extra-articular (systemic) manifestations [Klein, Molad, 2021, p. 403]. One of the least studied yet clinically important aspects of RA is derangement of the hematologic system, including changes in platelet number and function. Unlike thrombocytosis, which is a fairly typical laboratory marker of high RA inflammatory activity and correlates with C-reactive protein and ESR levels, thrombocytopenia is considerably less common in this disease and is therefore often dismissed by clinicians as an incidental finding unrelated to the underlying condition.

Nevertheless, the clinical significance of thrombocytopenia in RA patients is substantial: it may be the first sign of a life-threatening treatment complication (agranulocytosis, pancytopenia due to cytostatic myelosuppression), a marker of an emerging secondary autoimmune syndrome (Felty syndrome, secondary antiphospholipid syndrome, immune thrombocytopenic purpura), the result of an intercurrent infection (including viral infection), a manifestation of a paraneoplastic process (T-cell large granular lymphocytic leukemia, myelodysplastic syndrome), or a consequence of thrombotic microangiopathy requiring emergency treatment [Fam, 2020, p. 3]. Misinterpretation of the nature of thrombocytopenia may lead either to unwarranted discontinuation of disease-modifying therapy with subsequent flare of the joint disease, or, conversely, to continued administration of a drug causing a life-threatening cytopenia.

The relevance of this problem is further heightened by the expanding range of drugs used in RA: alongside conventional synthetic disease-modifying antirheumatic drugs (methotrexate, leflunomide, sulfasalazine, gold salts, D-penicillamine), biologic disease-modifying antirheumatic drugs (tumor necrosis factor-alpha inhibitors, anti-CD20 therapy, interleukin-6 inhibitors) and targeted synthetic agents (Janus kinase inhibitors) are increasingly used, each with its own hematologic toxicity profile [Bobircă, 2022, p. 4]. In addition, increased life expectancy of RA patients and the accumulation of comorbidities raise the likelihood of independent hematologic disease developing in parallel, clinically mimicking RA-related thrombocytopenia.

The aim of this review is to systematize current data on the etiology, pathogenesis, clinical and laboratory presentation, and differential diagnostic algorithms for thrombocytopenia in patients with rheumatoid arthritis, and to formulate practical recommendations for a stepwise diagnostic work-up applicable in the practice of rheumatologists, hematologists, and internists.

To achieve this aim, data published in the PubMed, Scopus, Google Scholar, ResearchGate, and Cyberleninka databases between 1988 and 2025 were analyzed, including original studies, case series, systematic reviews, and clinical guidelines addressing the hematologic manifestations of rheumatoid arthritis.

The literature search methodology included a targeted search for publications using the keywords “rheumatoid arthritis thrombocytopenia,” “Felty syndrome,” “drug-induced thrombocytopenia DMARD,” “methotrexate myelotoxicity,” “thrombotic microangiopathy rheumatoid arthritis,” and “antiphospholipid syndrome thrombocytopenia,” followed by selection of studies

containing original clinical, laboratory, or pathogenetic data. From the initially identified sources, publications meeting reliability criteria (peer-reviewed journals, indexing in international databases) and thematic relevance were selected for final analysis. Particular attention was paid to studies providing comparative clinical and laboratory characteristics of different causes of thrombocytopenia, as such data are of the greatest practical value in constructing a differential diagnostic algorithm.

The structure of this review follows a nosological principle: after a general characterization of the epidemiology of thrombocytopenia in RA, drug-induced, immune, paraneoplastic, infectious, and artefactual causes of reduced platelet count are sequentially considered, followed by a generalized differential diagnostic algorithm and comparative tables summarizing the key clinical and laboratory features of each condition.

LITERATURE REVIEW

1. General characteristics and epidemiology of thrombocytopenia in RA

Thrombocytopenia is defined as a peripheral blood platelet count below 150×10^9/L; a count of $70–150\times10^9$/L is considered mild, and a count below 20×10^9/L is considered severe [Bobircă, 2022, p. 2]. According to large-scale reviews, the prevalence of thrombocytopenia among RA patients ranges from 3% to 10%, considerably lower than the prevalence of thrombocytosis, which is recorded in nearly half of patients with high disease activity [Naz, 2001, p. 112]. This asymmetry is explained by the fact that chronic inflammation itself stimulates megakaryocytopoiesis through pro-inflammatory cytokines (interleukin-6, thrombopoietin), whereas a true reduction in platelet count is more often associated with an additional pathogenic mechanism — drug-related, autoimmune, infectious, or neoplastic.

Klein and Molad (2021) emphasize that hematologic disorders in rheumatic diseases are frequently the first clinical manifestation of the disease or a marker of its exacerbation, and therefore differential diagnosis of cytopenias should be conducted jointly by rheumatologists and hematologists [Klein, Molad, 2021, p. 404]. The authors note that, apart from systemic lupus erythematosus, in which cytopenias are the most common among rheumatic diseases, a significant contribution to the spectrum of hematologic disorders is made by RA (Felty syndrome, drug-induced cytopenias) and antiphospholipid syndrome (thrombocytopenia, thrombotic microangiopathy) [Klein, Molad, 2021, p. 407].

It is important to bear in mind that interpretation of platelet counts in an RA patient is impossible outside the context of disease activity and ongoing therapy. During a flare of joint disease accompanied by elevated acute-phase proteins, most patients show an elevated or high-normal platelet count owing to the stimulatory effect of interleukin-6 on hepatic thrombopoietin production and, consequently, on bone marrow megakaryocytopoiesis. For this reason, the detection of thrombocytopenia in a patient with formally high RA inflammatory activity should be perceived by the clinician as a discordant, alarming laboratory finding that mandates clarification of its cause rather than being automatically attributed to the underlying disease. This point is of fundamental importance for clinical vigilance, since in practice the opposite situation is often observed: a decrease in platelet count is mistakenly regarded as a variant of RA course and is not subjected to targeted diagnostic evaluation, which may lead to delayed diagnosis of potentially dangerous conditions, including hematologic malignancies and thrombotic microangiopathy.

From a clinical and epidemiological standpoint, gender- and age-related features should also be considered: since RA as a whole more frequently develops in middle-aged women, and the disease duration by the time complications such as Felty syndrome develop usually exceeds 10 years, the group most vulnerable to immune-mediated causes of thrombocytopenia comprises middle-aged and older female patients with a long history of seropositive erosive RA, whereas drug-induced thrombocytopenia may develop at any stage of the disease, including early stages of methotrexate therapy [Fujita, 2023, p. 2].

2. Pathogenetic classification of the causes of thrombocytopenia in RA

From a pathogenetic standpoint, all causes of thrombocytopenia in RA patients can be divided into several broad groups: 1) drug-induced (the most common), 2) immune-mediated, not directly related to drug intake, 3) related to Felty syndrome and related conditions, 4) related to thrombotic microangiopathy and secondary antiphospholipid syndrome, 5) infectious (including virus-associated), 6) neoplastic and myelodysplastic, 7) related to hypersplenism and portal hypertension, and 8) pseudothrombocytopenia (a laboratory artifact) [Fulga et al., 2022, p. 3].

2.1. Drug-induced thrombocytopenia

The most common cause of thrombocytopenia in RA patients is drug-induced myelosuppression associated with the use of disease-modifying antirheumatic drugs — methotrexate, leflunomide, and sulfasalazine — as well as biologic and targeted synthetic agents [Fulga et al., 2022, p. 4]. Two fundamentally different mechanisms of drug-induced thrombocytopenia are recognized: direct bone marrow toxicity, leading to suppression of megakaryocyte production, and an immune-mediated mechanism, in which drug-dependent antibodies bind to membrane glycoproteins on platelets (predominantly GP IIb/IIIa or GP Ib/IX), resulting in accelerated platelet destruction, mainly in the spleen [Fulga et al., 2022, p. 4].

Methotrexate remains the first-line disease-modifying drug for RA; however, long-term use, even at low doses, may be complicated by myelotoxicity, including thrombocytopenia. In a classic study by Owlia and colleagues involving 315 patients receiving low-dose methotrexate, thrombocytopenia ($\leq100\times10^9$/L) was detected in 13 patients (4.1%), and its development was significantly associated with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), which can potentiate methotrexate toxicity through competitive displacement from plasma protein binding and reduced renal clearance [Owlia, 1996, p. 1]. The myelotoxic mechanism of methotrexate on the megakaryocyte lineage is related to inhibition of dihydrofolate reductase, disruption of thymidylate and purine synthesis, and consequent blockade of cell proliferation [Bhatt, 2013, p. 2]. Experimental data also indicate that methotrexate can

induce apoptosis of mature platelets via JNK-mediated mitochondrial damage, which supplements the myelosuppressive mechanism with peripheral destruction of already formed cells [Kar, 2015, p. 1]. Rarer, more severe forms of toxicity have also been described — methotrexate-induced hypoplastic myelodysplasia with pancytopenia, requiring complete drug discontinuation and intensive supportive care [Bhoi, 2023, p. 1].

Combination therapy with methotrexate and leflunomide, used when monotherapy is insufficiently effective, is associated with an increased risk of hepatotoxicity and, in rare cases, with the development of thrombotic microangiopathy — a condition clinically indistinguishable from thrombotic thrombocytopenic purpura and requiring immediate discontinuation of both drugs [Rüth, 2020, p. 1]. In a case reported in the literature, a patient receiving combination therapy developed acute liver failure, acute kidney injury, thrombocytopenia, and Coombs-negative hemolytic anemia with schistocytosis and reduced ADAMTS13 activity, underscoring the need to exclude secondary thrombotic microangiopathy whenever thrombocytopenia appears during combination disease-modifying therapy [Rüth, 2020, p. 2].

Leflunomide, an inhibitor of pyrimidine nucleotide synthesis, has its own hematologic toxicity profile independent of methotrexate, although isolated thrombocytopenia during leflunomide monotherapy is reported less frequently than with methotrexate. The drug's active metabolite, A771726, has a long half-life (up to two weeks), resulting in prolonged persistence of toxic effects even after discontinuation and necessitating a "washout" procedure with cholestyramine or activated charcoal in cases of severe cytopenia [Rüth, 2020, p. 3]. Sulfasalazine, used both as monotherapy and in combination with other disease-modifying drugs, can cause idiosyncratic (non-dose-dependent) thrombocytopenia, believed to have an immunoallergic basis; a characteristic feature of this reaction is its onset within the first weeks to months of therapy and, as a rule, complete resolution after drug discontinuation. Gold salts and D-penicillamine, historically widely used in RA, are now used considerably less often but retain clinical relevance as classic causes of immune thrombocytopenia associated with anti-platelet antibody formation.

An important practical implication of these data is the need to distinguish between two fundamentally different management scenarios for drug-induced thrombocytopenia: dose-dependent myelotoxic thrombocytopenia, which usually resolves with dose reduction and correction of concomitant therapy (in particular, discontinuation of NSAIDs that potentiate toxicity), and idiosyncratic immune-mediated thrombocytopenia, which requires complete and unconditional discontinuation of the causative drug, with its future re-administration contraindicated because of the risk of a repeat, often more severe reaction upon re-exposure to the antigen.

Biologic therapy can also induce severe thrombocytopenia, although such cases are reported considerably less often than drug-induced neutropenia. Liao and colleagues (2022) described a case of severe, refractory thrombocytopenia in an RA patient receiving adalimumab (a tumor necrosis factor-alpha inhibitor): after four injections of the drug, the platelet count fell to 4×10^9/L, and subsequent treatment with glucocorticoids, recombinant thrombopoietin, and platelet transfusions produced only a partial and unsustained response [Liao, 2022, p. 1]. The authors note that repeat bone marrow examination in this patient revealed no significant abnormalities, pointing to a predominantly peripheral (immune) rather than central mechanism of TNF-alpha-inhibitor-induced thrombocytopenia and underscoring the need for continued vigilance even in the absence of typical myelosuppressive findings on bone marrow examination [Liao, 2022, p. 2].

A meta-analysis of randomized controlled trials examining cytopenias during methotrexate therapy in patients with rheumatic diseases also confirmed a statistically significant increase in the risk of thrombocytopenia compared with placebo, although the absolute frequency of severe forms remains low [Vanni, Lyu, Solomon, 2022, p. 1]. At the same time, retrospective registry studies on neutropenia associated with biologic therapy in patients with rheumatic diseases show that different classes of biologic agents (TNF-alpha inhibitors, anti-CD20 therapy, interleukin-6 receptor inhibitors) differ substantially in their hematologic toxicity profiles, making it unjustified to extrapolate data obtained for one drug class to the entire spectrum of biologic therapy [Espinoza, Le Blay, Combe, 2017, p. 845]. Janus kinase (JAK) inhibitors, a relatively new class of targeted synthetic disease-modifying drugs, are also associated with a dose-dependent risk of cytopenias, including thrombocytopenia, as reflected in the respective prescribing information and necessitating regular laboratory monitoring, particularly during the first months of therapy.

2.2. Immune thrombocytopenia (ITP) associated with RA

The coexistence of RA with idiopathic (primary) immune thrombocytopenic purpura has been recognized in the literature for some time, although it remains a rare finding. In a review of five clinical cases and the relevant literature, Naz and colleagues showed that all patients with concomitant RA and ITP had elevated platelet-associated immunoglobulin G (PAIgG) levels, while bone marrow examination demonstrated compensatory megakaryocytic hyperplasia with a normal or increased number of megakaryocytes, confirming a peripheral (destructive) rather than central (productive) mechanism of thrombocytopenia [Naz, 2001, p. 113]. The authors emphasize that a diagnosis of autoimmune thrombocytopenia in RA is one of exclusion and should be established only after drug-induced, infectious, and neoplastic causes of cytopenia have been ruled out [Naz, 2001, p. 115].

Clinically, it is important to distinguish between: 1) a true coexisting (comorbid) ITP, not directly pathogenetically related to RA but statistically more common in patients with autoimmune disease in general, and 2) secondary autoimmune thrombocytopenia, pathogenetically linked to the production of anti-platelet autoantibodies within the systemic autoimmune process of RA, analogous to what occurs in systemic lupus erythematosus [myITPcenter, 2023, p. 1]. Clinically, both variants present with a hemorrhagic syndrome of varying severity — from an asymptomatic laboratory finding and petechial rash on the lower legs to a fully developed hemorrhagic syndrome with gingival and epistaxis bleeding and, in severe cases, intracranial hemorrhage.

2.3. Felty syndrome and related lymphoproliferative conditions

Felty syndrome (FS), first described by the American physician Augustus Roi Felty in 1924, is classically defined by a triad of long-standing seropositive RA, splenomegaly, and neutropenia [Fam, 2020, p. 1; Fujita, 2023, p. 1]. It typically develops no earlier than 10 years after the onset of joint disease and occurs in fewer than 1–3% of RA patients; the incidence of FS has decreased substantially since methotrexate came into widespread clinical use [Fujita, 2023, p. 1]. Although neutropenia remains the predominant hematologic manifestation of the syndrome, a substantial proportion of patients also present with anemia and thrombocytopenia, as well as lymphadenopathy, hepatomegaly, leg ulcers, and, in some cases, portal hypertension secondary to nodular regenerative hyperplasia of the liver [Palit, 2020, p. 1].

Diagnostic criteria for FS include: 1) confirmed RA meeting classification criteria; 2) splenomegaly, confirmed by physical examination or imaging; 3) leukopenia (<4.0×10⁹/L), neutropenia (<2.0×10⁹/L), or thrombocytopenia (<100×10⁹/L); and 4) absence of other established causes of cytopenia (e.g., drug-induced) or splenomegaly (e.g., lymphoma) [Zhang, 2020, p. 2]. It is important to note that not all components of the triad need to be present simultaneously for the diagnosis to be established — neutropenia is regarded as the obligatory but not sole criterion, whereas thrombocytopenia and anemia may be absent in some patients [Palit, 2020, p. 1].

The pathogenesis of FS remains incompletely understood; proposed mechanisms include Fas-mediated apoptosis of neutrophils, formation of anti-neutrophil antibodies and antibodies to granulocyte colony-stimulating factor, increased neutrophil consumption within the context of NETosis, and suppression of granulopoiesis by T cells with a large granular lymphocyte (T-LGL) phenotype [Fam, 2020, p. 2]. This latter mechanism underlies the widely discussed concept of a shared pathogenetic spectrum encompassing "FS — T-cell large granular lymphocytic leukemia" (T-LGL leukemia): the clinical manifestations of both conditions — neutropenia, splenomegaly, and arthritis — may be indistinguishable, and a proportion of cases previously classified as FS are, upon detailed immunophenotyping and T-cell receptor clonality studies, found to represent true T-LGL leukemia [Cook, 2023, p. 1; Gorodetskiy, 2021, p. 148]. In a cohort study by Gorodetskiy and colleagues (2021) from a single institution, a substantial proportion of patients with an initial diagnosis of FS were found on molecular genetic testing to harbor a clonal T-LGL population, underscoring the need for flow cytometry and T-cell receptor gene rearrangement studies in all patients with suspected FS [Gorodetskiy, 2021, p. 150].

Differential diagnosis of FS should include exclusion of infectious diseases and lymphoproliferative and myeloproliferative neoplasms, as well as other systemic connective tissue diseases, since splenomegaly and cytopenias are a common feature shared by a wide range of conditions [Fam, 2020, p. 3]. Treatment of FS has not yet been standardized owing to the absence of randomized controlled trials; methotrexate remains the first-choice agent, with rituximab considered in refractory cases, whereas TNF-alpha inhibitors may paradoxically worsen neutropenia and are therefore prescribed with caution [Fam, 2020, p. 4; Narváez, 2018, p. 3].

2.4. Secondary antiphospholipid syndrome and thrombotic microangiopathy

Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, anti-beta-2-glycoprotein I antibodies) are detected in a subset of RA patients, potentially indicating the development of secondary antiphospholipid syndrome (APS) — a condition combining recurrent thrombosis and/or obstetric complications with persistent circulating antiphospholipid antibodies [Klein, Molad, 2021, p. 408]. Thrombocytopenia in secondary APS is usually moderate (70–120×10⁹/L) and rarely accompanied by significant hemorrhagic manifestations, since the disease is fundamentally a prothrombotic rather than a hemorrhagic disorder of hemostasis [Klein, Molad, 2021, p. 409].

The most severe manifestation of APS is catastrophic antiphospholipid syndrome — an acute multi-organ thrombotic microangiopathy with high mortality, requiring emergency combination therapy (anticoagulants, glucocorticoids, plasmapheresis, intravenous immunoglobulin) [Klein, Molad, 2021, p. 410]. Thrombotic microangiopathy in RA patients may also be drug-related, as demonstrated in the observation by Rüth and colleagues during combination therapy with leflunomide and methotrexate, in which reduced ADAMTS13 activity and schistocytosis on peripheral blood smear were identified — classic laboratory markers allowing differentiation of thrombotic microangiopathy from other causes of thrombocytopenia [Rüth, 2020, p. 2].

2.5. Infectious and virus-associated causes

An intercurrent infection is a common cause of acute-onset thrombocytopenia in RA patients receiving immunosuppressive therapy. Particular attention in recent years has been paid to thrombocytopenia associated with SARS-CoV-2 infection. Bobircă and colleagues (2022) described a case of severe immune-mediated thrombocytopenia in a patient with active RA in the setting of COVID-19, emphasizing that viral infection can stimulate the immune system to destroy platelets through enhanced autoantibody and immune complex production, with the severity of thrombocytopenia correlating with the severity of infection and serving as an unfavorable prognostic factor [Bobircă, 2022, p. 1]. The authors point to shared pathogenetic mechanisms — molecular mimicry, expression of cryptic antigens, and epitope spreading — as the link between viral infection and exacerbation of the autoimmune process [Bobircă, 2022, p. 3]. The practical implication of this observation is the need for temporary discontinuation of leflunomide, methotrexate, and sulfasalazine in cases of confirmed or suspected SARS-CoV-2 infection, given the risk of potentiated myelotoxicity and immunosuppression [Bobircă, 2022, p. 5].

In addition to SARS-CoV-2, other viral agents capable of causing thrombocytopenia in RA patients include Epstein-Barr virus, cytomegalovirus, hepatitis B and C viruses, HIV, and parvovirus B19, which can also induce transient erythroid aplasia. Bacterial

infections, including sepsis, cause thrombocytopenia through increased platelet consumption in the setting of disseminated intravascular coagulation (DIC), as well as through direct bone marrow suppression during severe systemic inflammatory response.

2.6. Neoplastic and myelodysplastic causes

Long-term methotrexate therapy, owing to its antiproliferative effect on rapidly dividing cells, rarely leads to the development of secondary hypoplastic myelodysplastic syndrome (MDS) with pancytopenia, including marked thrombocytopenia [Bhoi, 2023, p. 1]. This condition presents clinically with progressive weakness, hemorrhagic syndrome, and recurrent infections, and requires mandatory morphological and cytogenetic bone marrow examination to confirm the diagnosis and exclude acute leukemia.

Particular attention should also be paid to the previously mentioned T-cell large granular lymphocytic (T-LGL) leukemia — a clonal lymphoproliferative disorder associated with RA in approximately 11–36% of cases (whereas the prevalence of RA in the general population does not exceed 1%), indicating a strong pathogenetic relationship between the two conditions [Loughran, 2023, p. 1]. Clinically, T-LGL leukemia is indistinguishable from FS and is characterized by neutropenia, splenomegaly, and arthritis; immunophenotyping of peripheral blood lymphocytes and study of clonal T-cell receptor rearrangement play a key role in differential diagnosis [Loughran, 2023, p. 2].

Finally, thrombocytopenia may be a paraneoplastic manifestation of solid tumors and lymphoproliferative diseases not directly pathogenetically linked to RA but statistically more common in patients receiving long-term immunosuppressive therapy, mandating oncologic vigilance whenever unexplained cytopenia occurs, particularly in combination with B-symptoms (fever, night sweats, weight loss) [András, 2006, p. 378].

2.7. Hypersplenism and portal hypertension

Splenomegaly, whether developing in the setting of FS or from other causes (portal hypertension, lymphoproliferative disease), can lead to hypersplenism — sequestration and pooling of blood cell elements, including platelets, in the enlarged spleen, resulting in moderate thrombocytopenia usually accompanied by anemia and/or leukopenia [Palit, 2020, p. 2]. Cases of porto-sinusoidal vascular disease (formerly termed idiopathic non-cirrhotic portal hypertension) have also been described in patients with longstanding FS, complicated by esophageal and gastric varices with a risk of bleeding, which substantially aggravates the severity of thrombocytopenia through the combined effect of hypersplenism and blood loss [Zhang, 2020, p. 1].

2.8. Pseudothrombocytopenia

A separate group comprises cases of so-called pseudothrombocytopenia — a laboratory artifact caused by in vitro platelet agglutination induced by ethylenediaminetetraacetic acid (EDTA), used as an anticoagulant for routine blood sampling. This phenomenon is related to the presence of EDTA-dependent anti-platelet autoantibodies in the patient and can mimic marked thrombocytopenia on automated cell counting, while the true platelet count remains normal. Excluding pseudothrombocytopenia by peripheral blood smear microscopy and/or repeat testing using sodium citrate as the anticoagulant is a mandatory first step in the diagnostic algorithm whenever unexpected thrombocytopenia is detected, as it prevents unwarranted diagnostic and therapeutic measures.

3. Clinical features of hemorrhagic syndrome across different types of thrombocytopenia

The clinical picture of hemorrhagic syndrome in RA patients with thrombocytopenia is determined not so much by the absolute platelet count as by the rate of its decline and the preserved functional activity of circulating cells. In slowly progressive, chronic thrombocytopenia (for example, in the setting of Felty syndrome or compensated hypersplenism), patients often remain asymptomatic even at platelet counts of 50–70×10⁹/L, as compensatory hemostatic mechanisms have time to develop. In contrast, an acute fall in platelet count (drug idiosyncrasy, thrombotic microangiopathy, severe immune thrombocytopenia) is accompanied by pronounced hemorrhagic manifestations even at relatively moderate reductions in platelet number.

Clinical manifestations of hemorrhagic syndrome include petechial and ecchymotic rash on the skin, predominantly at sites of pressure from clothing and on the lower extremities, gingival bleeding, epistaxis, menorrhagia in women of reproductive age, and, in severe cases, gastrointestinal bleeding and intracranial hemorrhage. It is worth noting separately that in RA patients on long-term glucocorticoid therapy, the clinical picture of hemorrhagic syndrome may be obscured by the "senile" purpura and increased capillary fragility characteristic of steroid therapy, which complicates clinical assessment of the true severity of thrombocytopenia based on physical findings alone and underscores the need for mandatory laboratory confirmation.

Accompanying symptoms provide an important clinical clue: fever, night sweats, and weight loss suggest a probable infectious or neoplastic origin of thrombocytopenia; recurrent thrombosis, livedo reticularis, and an obstetric history of recurrent pregnancy loss suggest secondary antiphospholipid syndrome; splenomegaly, recurrent bacterial infections, and leg ulcers suggest Felty syndrome; and neurological symptoms, fever, renal failure, and microangiopathic hemolytic anemia (the classic pentad) suggest thrombotic microangiopathy requiring emergency intervention.

4. The role of laboratory and instrumental methods in differential diagnosis

Comprehensive laboratory evaluation is of key importance for the differential diagnosis of thrombocytopenia in RA and should include a complete blood count with reticulocyte count and peripheral smear microscopy (assessment of platelet morphology, presence of schistocytes, blast cells, atypical lymphocytes), biochemical testing (lactate dehydrogenase, bilirubin, haptoglobin — markers of hemolysis), coagulation studies, a direct Coombs test, measurement of platelet-associated antibodies and antiphospholipid antibodies, ADAMTS13 activity, and, when indicated, morphological and immunophenotypic examination of the bone marrow

[Klein, Molad, 2021, p. 405; Naz, 2001, p. 114]. Imaging methods (abdominal ultrasound, computed tomography) are used to assess spleen and liver size, detect lymphadenopathy, and identify signs of portal hypertension.

DISCUSSION

The literature analysis performed demonstrates that thrombocytopenia in RA is not an independent nosological entity but a heterogeneous clinical and laboratory syndrome requiring a systematic diagnostic approach. Three main diagnostic scenarios are of particular importance for clinical practice.

First, the most common and potentially reversible scenario remains drug-induced thrombocytopenia associated with disease-modifying antirheumatic drugs, primarily methotrexate, especially with concomitant NSAID use, which potentiates its toxicity [Owlia, 1996, p. 1]. In such cases, timely discontinuation or dose adjustment of the drug usually leads to rapid platelet count recovery, underscoring the importance of regular laboratory monitoring in all patients receiving disease-modifying therapy.

Second, particular diagnostic attention should be paid to a group of immune-mediated conditions — true and secondary ITP, Felty syndrome, and secondary APS — in which discontinuation of disease-modifying therapy not only fails to resolve thrombocytopenia but may also provoke a flare of joint disease without hematologic improvement. In such situations, a pathogenetically directed rather than empirical approach is essential: use of glucocorticoids, targeted immunosuppressants (rituximab), or anticoagulant therapy where APS is confirmed [Fam, 2020, p. 4].

Third, an essential task of differential diagnosis remains the timely recognition of life-threatening conditions requiring a fundamentally different approach — thrombotic microangiopathy, acute leukemia, myelodysplastic syndrome, and T-LGL leukemia — which may masquerade as typical RA-related thrombocytopenia but require emergency (thrombotic microangiopathy) or specialized hemato-oncologic (MDS, leukemia) management [Rüth, 2020, p. 2; Loughran, 2023, p. 2].

A particularly debated issue is the concept of a shared pathogenetic spectrum encompassing "FS — T-LGL leukemia," actively discussed in the contemporary literature. On the one hand, the considerable clinical and laboratory overlap between the two conditions complicates their differentiation using routine investigations alone; on the other hand, the therapeutic approach to true clonal T-LGL leukemia (low-dose immunosuppressants, methotrexate, cyclophosphamide) largely overlaps with the management of FS, which somewhat reduces the clinical significance of strict nosological differentiation in the initial stages of patient management, while retaining fundamental importance for long-term prognosis and oncologic vigilance [Gorodetskiy, 2021, p. 151; Cook, 2023, p. 2].

A limitation of most of the sources analyzed is their predominantly descriptive nature — case series and retrospective cohorts — related to the relative rarity of thrombocytopenia in RA and, consequently, the absence of large prospective randomized trials specifically addressing this problem. This limits the ability to develop evidence-based clinical recommendations and accounts for the persisting variability in diagnostic and therapeutic approaches across different clinical centers.

Particular discussion is warranted regarding the management of disease-modifying therapy in RA when thrombocytopenia of unclear origin is detected. On the one hand, premature discontinuation of all potentially myelotoxic drugs before the diagnostic work-up is complete often leads to flare of joint disease and reduced quality of life without a guaranteed improvement in hematologic parameters if the true cause of thrombocytopenia is unrelated to drug therapy. On the other hand, continuing a potentially causative drug pending final diagnosis carries the risk of progression of cytopenia to life-threatening levels. A differentiated approach appears optimal: in mild thrombocytopenia (100–150×10⁹/L) with a stable clinical condition, continuation of therapy is acceptable with more frequent laboratory monitoring alongside diagnostic work-up; in moderate to severe thrombocytopenia (below 100×10⁹/L), particularly when accompanied by clinical hemorrhagic manifestations, temporary discontinuation of the most likely causative drug is advisable, with subsequent assessment of platelet count trends serving as a diagnostic test ex juvantibus that complements laboratory findings.

It should also be noted that the vast majority of the publications analyzed originate from Western Europe, North America, and East Asia, whereas data on the structure of causes of thrombocytopenia in RA populations in Central Asia, including Uzbekistan, are extremely limited in the available literature. Given possible ethnic and population differences in the frequency of specific HLA alleles associated with severe erosive RA and Felty syndrome, as well as differences in the availability and patterns of use of disease-modifying and biologic therapy, local epidemiological studies would be valuable to clarify the regionally relevant structure of causes of thrombocytopenia in RA patients and to adapt the proposed diagnostic algorithm to local resource constraints.

RESULTS

Based on the literature analysis, the main causes of thrombocytopenia in RA, their pathogenetic mechanisms, and characteristic clinical and laboratory features have been systematized, and a differential diagnostic algorithm has been proposed.

Table 1. Comparative characteristics of the main causes of thrombocytopenia in rheumatoid arthritis

№	Cause	Pathogenetic mechanism	Severity of thrombocytopenia	Associated blood changes	Key diagnostic markers
1	Drug-induced (methotrexate, leflunomide, sulfasalazine)	Direct myelosuppression, platelet apoptosis	Mild–moderate, occasionally severe	Possible anemia, leukopenia (pancytopenia with severe toxicity)	Association with dose and duration; response to drug withdrawal

№	Cause	Pathogenetic mechanism	Severity of thrombocytopenia	Associated blood changes	Key diagnostic markers
2	Immune thrombocytopenia (ITP), including drug-dependent	Anti-platelet (including drug-dependent) antibodies, splenic destruction	Moderate–severe	Isolated thrombocytopenia	Elevated PAIgG, megakaryocytic hyperplasia on bone marrow examination
3	Felty syndrome	Fas-mediated apoptosis, anti-G-CSF antibodies, T-LGL-mediated suppression of granulopoiesis	Mild–moderate	Neutropenia (obligatory), anemia, splenomegaly	RA–splenomegaly–neutropenia triad, HLA-DR4
4	T-LGL leukemia	Clonal T-LGL proliferation, suppression of hematopoiesis	Mild–moderate	Neutropenia, lymphocytosis with large granular lymphocytes	Clonal TCR gene rearrangement, immunophenotyping
5	Secondary antiphospholipid syndrome	Immune platelet destruction, microthrombosis	Moderate	History of thrombosis, recurrent pregnancy loss	Lupus anticoagulant, anticardiolipin and anti-β2-GPI antibodies
6	Thrombotic microangiopathy	ADAMTS13 deficiency/inhibition, endothelial injury	Severe	Hemolytic anemia, schistocytosis, elevated LDH	Reduced ADAMTS13 activity, negative Coombs test
7	Viral infections (SARS-CoV-2, EBV, CMV, parvovirus B19)	Immune-mediated destruction, bone marrow suppression	Variable	Lymphopenia, signs of infection	PCR/serology for the causative agent, correlation with infection severity
8	Myelodysplastic syndrome	Bone marrow dysplasia, ineffective hematopoiesis	Moderate–severe, pancytopenia	Anemia, leukopenia, dysplastic cell changes	Bone marrow morphology and cytogenetics
9	Hypersplenism / portal hypertension	Splenic platelet sequestration	Mild–moderate	Anemia, leukopenia, esophageal varices	Splenomegaly on ultrasound/CT, signs of portal hypertension
10	Pseudothrombocytopenia	EDTA-dependent in vitro platelet agglutination	“Falsely” severe	None	Normal platelet count on repeat testing with citrate

Table 2. Stages of laboratory evaluation of an RA patient with newly detected thrombocytopenia

Stage	Action	Diagnostic purpose
1	Repeat blood count using sodium citrate; peripheral smear microscopy	Exclude pseudothrombocytopenia
2	Review of medications and doses; assessment of temporal association	Confirm/exclude drug-induced thrombocytopenia
3	Complete blood count, reticulocytes, LDH, bilirubin, haptoglobin, Coombs test	Exclude hemolysis and thrombotic microangiopathy
4	Abdominal ultrasound	Assess spleen and liver size, signs of portal hypertension
5	Antiphospholipid antibody testing	Exclude secondary APS
6	Viral work-up (PCR/serology)	Exclude virus-associated thrombocytopenia
7	PAIgG and antinuclear antibody testing	Confirm immune-mediated thrombocytopenia
8	Lymphocyte immunophenotyping, TCR gene rearrangement studies	Exclude T-LGL leukemia
9	Bone marrow morphology and cytogenetics	Exclude MDS and acute leukemia; confirm megakaryocytic hyperplasia
10	ADAMTS13 activity, schistocytes on smear	Confirm/exclude thrombotic microangiopathy

As the algorithm above shows, the key decision points in the diagnostic pathway are: 1) exclusion of a laboratory artifact; 2) assessment of the temporal relationship with drug intake; 3) identification of features of microangiopathic hemolysis requiring

emergency measures; 4) evaluation of spleen size and presence of neutropenia to exclude FS and T-LGL leukemia; and 5) a targeted immunologic and hematologic search when no obvious cause is identified.

The systematic analysis performed shows that the most common cause of thrombocytopenia in RA identified in the analyzed sources remains drug-induced myelosuppression (accounting for an estimated 40–60% of all cases of thrombocytopenia in RA patients across different reports), while true autoimmune thrombocytopenia, Felty syndrome, and thrombotic microangiopathy together account for a smaller but clinically most significant proportion, given the severity of their course and the need for specialized treatment [Fulga et al., 2022, p. 5; Naz, 2001, p. 112].

CONCLUSION

Thrombocytopenia in patients with rheumatoid arthritis represents a multifactorial syndrome whose differential diagnosis requires a consistent and systematic approach. The literature analysis performed allows the following main conclusions to be drawn.

1. Thrombocytopenia in RA is considerably less common than thrombocytosis, with a reported prevalence ranging from 3% to 10% across different sources; drug-induced myelosuppression, primarily related to methotrexate use, especially in combination with NSAIDs, remains the leading cause.
2. Alongside drug-induced thrombocytopenia, immune-mediated conditions — secondary and comorbid immune thrombocytopenia, Felty syndrome, and secondary antiphospholipid syndrome — are of considerable clinical importance and require a fundamentally different, pathogenetically directed therapeutic approach.
3. Particular diagnostic attention should be paid to life-threatening conditions — thrombotic microangiopathy and acute hematologic malignancies (myelodysplastic syndrome, T-cell large granular lymphocytic leukemia) — which may clinically mimic typical RA-related thrombocytopenia but require emergency or specialized hemato-oncologic management.
4. The first and mandatory step in the diagnostic work-up of unexpected thrombocytopenia should be the exclusion of pseudothrombocytopenia — a laboratory artifact related to EDTA-dependent platelet agglutination.
5. The stepwise diagnostic algorithm proposed in this review, based on sequential assessment of drug history, features of hemolysis, splenomegaly, and the results of targeted immunologic and hematologic evaluation, may serve as a practical tool for rheumatologists, hematologists, and internists in managing RA patients with newly detected thrombocytopenia.
6. Given the predominantly descriptive nature of the available data, prospective multicenter studies are warranted to clarify the true prevalence and structure of the causes of thrombocytopenia in RA, and to develop evidence-based clinical guidelines for the diagnosis and management of this condition.

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