The Blood in Rheumatology

13

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13.1 Introduction

Hematologic disorders including anemia, white blood cells abnormalities, platelet abnormalities, coagulopathy, and hematologic malignancies can be manifested in many autoimmune rheumatic diseases [1].

This chapter discusses the most common hematological abnormalities in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It also provides a simple approach to evaluate hematological abnormalities in patients with RA or SLE. This approach includes the most common causes, differential diagnosis, treatment, and prevention, with a special emphasis on ruling out life-threatening and urgent conditions.

13.2 Objectives

- Describe hematological manifestations of rheumatic diseases including different types of anemia, white blood cells, and platelets abnormalities, with brief about malignancies in rheumatoid arthritis.

- Construct a diagnostic approach to anemia in rheumatoid arthritis.
- Describe hematological manifestations of systemic lupus erythematosus including different types of anemia, white blood cells, and platelets abnormalities, with brief about lymphadenopathy, splenomegaly, and antibodies to clotting factors and antiphospholipids.
- Construct a diagnostic approach to anemia in systemic lupus erythematosus.
- Describe macrophage activation syndrome (MAS), and construct a diagnostic approach to it.

13.3 Hematological Manifestations of Rheumatoid Arthritis (RA)

13.3.1 Introduction

A review of hematologic involvement in RA is presented here, with an algorithm constructing a simple approach to RA patients with hematological manifestations (causes, diagnosis, and treatment) which is shown in Fig. 13.1.

13.3.1.1 Anemia

Anemia of chronic disease (ACD) and iron deficiency anemia (IDA) are considered the most common hematologic manifestations in patients with rheumatic diseases [2], with an estimated

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Fig. 13.1 Algorithmic approach for hematological manifestations of rheumatoid arthritis (RA). Classified by the affected component of the blood (platelets, HB, or WBC), in this approach; the authors suggest to broaden the differential diagnosis and to rule out non-rheumatological causes of mentioned abnormalities, including systemic diseases, infections, and drug-induced and primary hematological diseases. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience (Abbreviations: RA rheumatoid

arthritis, *R/O* rule out, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *TSH* thyroid stimulating hormone, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalization ratio, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *ITP* immune thrombocytopenic purpura, *TTP* thrombotic thrombocytopenic purpura, *H. pylori* *Helicobacter pylori*, *WBC* white blood cell, *HB* hemoglobin, *2ry* secondary, *-ve* negative, *+ve* positive)

prevalence in RA (30%–70%) in different studies [3, 4].

Anemia of Chronic Disease (ACD)

The ACD is associated with the following laboratory abnormalities:

- Mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) are usually normal (normocytic and normochromic) but may decrease due to concurrent iron deficiency, often to values characteristic of microcytic hypochromic anemia.
- The ferritin level is usually high with low serum levels of transferrin and iron [5].
- Bone marrow biopsy usually shows the presence of hemosiderin and normal cellularity, with increased numbers (in most cases) of plasma cells that are associated with lymphoid

aggregates. However, these findings are unpredictable and usually represent the various etiologies of cytopenias in RA patients.

The pathogenesis of the ACD is not entirely known. There are two major reasons seem to be of significant: defect in hemoglobin synthesis due to the diminished available iron secondary to iron trapping in macrophages and difficulty in bone marrow to produce more red blood cells in response to the anemia [6]. Immune mediators, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1, interleukin-6, interleukin-10, and interferon gamma, have great impact on these changes [6, 7]. Hepcidin, that is produced by the liver in response to inflammation, may have a great role in ACD, as it decreases iron absorption in the intestines and iron release from macrophages.

Low levels of erythropoietin and decreased response to erythropoietin may lead to the anemia in RA; these findings led to using erythropoietin in such patients which resulted in some increase in hemoglobin levels in few patients with improvement in arthritis symptoms [2, 8, 9].

Since the anemia may correlate with RA activity, patients may need higher doses of erythropoietin, which a medication with a high cost [10]. Hence, it should be considered only for patients with severe symptomatic anemia [11].

In the algorithm provided, if RA patient presents with normocytic normochromic anemia without hemolytic manifestations (normal levels

of LDH and reticulocyte and negative Coombs' test) and no other obvious inflammatory causes, patient should be treated with iron supplement and disease modifying anti-rheumatic drugs (DMARDs), and consider erythropoietin for symptomatic anemia (Fig. 13.2).

Iron Deficiency Anemia (IDA)

Iron deficiency anemia can be seen in up to 50% to 75% of RA patients who have chronic active disease [12].

It is mostly caused by chronic blood loss from gastritis (induced by prednisone [13] and/or non-steroidal anti-inflammatory drugs), peptic ulcer, or gastro esophageal reflux.

Fig. 13.2 Algorithmic approach for anemia in RA patients. In this approach the authors classified the anemia according to MCV and MCH, aiming to widen the differential diagnosis and to include non-rheumatological causes and co-factors. The evidence to support this approach is based on cumulative literature, current guide-

lines, and the author's experience (Abbreviations: *HB* hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *LDH* lactate dehydrogenate, *-ve* negative, *+ve* positive, *DMARD* disease-modifying anti-rheumatic drugs, *AIHA* autoimmune hemolytic anemia, *2ry* secondary)

As with all patients, occult blood in stool should not be neglected. All RA patients with IDA, epigastric pain, and/or occult blood in the stool should undergo upper gastrointestinal endoscopic examination.

Making the diagnosis of IDA among RA patients could be challenging, since the routine laboratory indices with mild to moderate iron deficiency may overlap with the ACD [14,15]. Thus, if iron deficiency is suspected, it may be most reliably verified by the absence of iron stores on bone marrow examination [14]. However, pursuing for bone marrow biopsy may be unnecessary if clear signs of iron deficiency such as a mean cell volume below 85, serum ferritin concentration below 40 mcg/L, and transferrin saturation $\leq 7\%$ are present [15].

RA patients frequently may have both IDA and ACD. In such case, the hemoglobin level usually decreases to below 9.5 g/dL, and the mean corpuscular volume is usually less than 80.

Measurement of serum soluble transferrin receptor (TfR) may be useful in differentiating IDA from anemia of chronic disease. [16].

Macrocytic Anemia

Less frequently, a megaloblastic anemia secondary to deficiency of folic acid or vitamin B12, methotrexate, or azathioprine is found in RA patients [2].

One study of 25 patients with RA noted vitamin B12 and folic acid deficiency in 29% and 21% of patients, respectively [2]. It was found that more than one type of anemia can present simultaneously in RA patients with anemia. Identifying each type could be masked by another.

Folic acid deficiency anemia in RA is usually due to the combination of increased requirements and reduced intake (e.g., pregnancy in a patient on a restricted diet) or to concurrent iron deficiency. On the other hand, there may be a genetic predisposition to develop macrocytosis and bone marrow toxicity with azathioprine. Approximately 0.3% of normal subjects have very low levels of thiopurine methyltransferase, one of the enzymes responsible for azathioprine metabolism. This abnormality is genetically determined and is linked to a higher risk of myelosuppression and macrocytic anemia [5].

The diagnosis is established by demonstrating a reduced folate level or vitamin B12 level, ; however, blood film is recommended to suggest the diagnosis and to rule out malignancies.

Hemolytic Anemia

Hemolytic anemia is not a typical feature of RA, although antibody-mediated, Coombs' positive hemolytic anemia has been described, primarily in Felty's syndrome [17].

Drug-induced hemolysis may also occur and is usually reversible when the offending drug is withdrawn, but most patients require corticosteroid therapy.

Bone Marrow Hypoplasia with Anemia

One of the serious hematologic complication of RA is bone marrow hypoplasia, ; luckily it is not frequently seen in RA patients. When present, it is mostly observed in association with Felty's syndrome, renal failure, and the administration of gold, penicillamine, azathioprine, cyclophosphamide, or other immunosuppressive agents.

Pure Red Cell Aplasia

This uncommon hematologic abnormality among RA patient should be suspected if the patient has severe normocytic normochromic anemia with very low absolute reticulocyte count without evidences of blood loss or hemolysis. Autoimmune suppression of erythroid stem cells, DMARDs, and parvovirus infection have been implicated in this complication [18], although single case report suggests that pure red cell aplasia could be an extraarticular manifestation of RA [19]. Isolated case reports have noted improvement in patients treated with corticosteroids, cyclophosphamide, azathioprine, or cyclosporine [20].

Treatment of Anemia in RA

Effective therapy of patient with RA and anemia is based upon an accurate determination of the cause of the anemia. As a result:

- Vitamin deficiencies leading to anemia should be corrected by the administration of folic acid or vitamin B12.
- Iron should not be given unless iron deficiency has been documented. It is recommended to

start with a combination of oral ferrous sulfate, which is usually given with 250 to 325 mg of ascorbic acid and on an empty stomach to enhance iron absorption. Alternatively, ferrous gluconate 300 mg three times daily may be used.

- Patients with persistent gastric intolerance to iron tablets may tolerate elixir of ferosol.
- If oral therapy fails, it is switched to intramuscular iron, and only very rarely parenteral iron as a slow IV infusion can be used.
- **Hemolysis** can be managed with corticosteroids (prednisone 60 mg/day).
- If no response is observed after 1 to 2 weeks, an immunosuppressive agent may be administered, such as azathioprine (50 to 150 mg/day).
- **DMARD-induced bone marrow suppression** should be treated by dose alteration or complete withdrawal of the suspected drug.
- **The ACD** often responds to therapy directed against RA, including DMARDs, and/or corticosteroids (prednisone at a dose of 0.5 to 1.0 mg/kg per day) [2].
- Several interventional studies have demonstrated the efficacy of erythropoietin in treating the anemia of RA [11]; however, only a limited number of patients with RA and ACD may require this treatment. High doses (300 to 800 units/kg/week given subcutaneously once or twice a week) are required, making this an expensive form of therapy. One specific role for erythropoietin among patients with RA is in the peri-operative management of anemia. Treating anemia in this setting may prevent the need for transfusion [2].

13.3.1.2 White Blood Cell (WBC) Count Abnormalities

Neutropenia and Felty's Syndrome

The principal leukopenic disorder among patients with RA is Felty's syndrome, which is defined as a triad of RA, splenomegaly, and neutropenia.

- Splenomegaly is not necessarily present [21].
- This disorder occurs in about 1% of patients with RA. Patients with this syndrome often has an advanced form of nodular RA, with high levels of rheumatoid factor.
- This disorder may be accompanied by severe infections, vasculitis, ulcers, neuropathic symptoms, interstitial lung disease, secondary Sjögren's syndrome, hepatomegaly, and lower extremity hyperpigmentation. These manifestations are rare in the current era of early aggressive therapy with DMARDs.

Although leukopenia is a common consequence of many rheumatic diseases, it is most frequently caused by the administration of DMARDs, including azathioprine, methotrexate, gold salts, sulfasalazine, and penicillamine [22, 23]. In addition, viral infections are another important differential diagnosis and should be excluded before considering the diagnosis of Felty's syndrome.

Management of Felty's syndrome is aimed at suppressing the inflammatory rheumatoid disease. There are several reports on the good outcome with use of gold salts, methotrexate, and biological therapy in these patients. In one retrospective review of all Felty's syndrome cases (1979 to 2003), it was concluded that Felty's syndrome is considered a mild disease and is not commonly linked to infectious complications. Gold is an effective treatment of Felty's syndrome [21].

Leukocytosis

Leukocytosis can occur during an inflammatory flare of RA. However, an associated bacterial infection must be considered and should be excluded in such patients.

Eosinophilia

Significant eosinophilia occurs in some patients with RA. It usually correlates with the presence of vasculitis, pleuropericarditis, pulmonary fibrosis, subcutaneous nodules, or gold-induced skin rashes [23].

13.3.1.3 Platelet Abnormalities

Thrombocytosis is common in RA, and a positive correlation has been found between the platelet count and disease activity. Extreme thrombocytosis has been noticed with extraarticular manifestations of the disease, particularly pulmonary involvement, peripheral neuropathy, and vasculitis [24]. The mechanism of thrombocytosis is unclear yet.

Thrombocytopenia is rare in RA, mostly induced by drug treatment such as gold, penicillamine, methotrexate, azathioprine, and TNF antagonists [25, 26]. Felty's syndrome, is another cause of thrombocytopenia in RA patients.

13.3.1.4 Hematological Malignancies in RA

Several studies have noted a higher risk of hematologic malignancy among RA patients contributing significantly to a higher morbidity and mortality of the disease [27–30]. Most large registries noted a higher risk for the development of lymphoproliferative diseases, particularly non-Hodgkin lymphoma (NHL). A study of nearly 18,000 RA patients noted a higher risk of lymphoma in patients with RA in comparison to the general population (the standardized incidence ratio or SIR) (SIR of 1.9) [31]. Although the risk in those treated with anti-tumor necrosis factor- α agents was greater than that for patients treated with methotrexate (SIRs of 2.9 and 1.7, respectively), the authors of the study noted that this difference could result if patients with active RA, who have a higher increased risk of developing lymphoma, were more often managed with anti-TNF therapy than those with less active RA.

The results of studies that have addressed the question of whether TNF inhibitor use is associated with increased cancer risk are mixed, and large observational studies were unable to demonstrate a significant increase in either hematologic malignancies or solid tumors for patients taking biologic DMARDs compared with those taking methotrexate [32, 33].

13.4 Hematological Manifestations of Systemic Lupus Erythematosus (SLE)

13.4.1 Introduction

Hematological involvement is commonly seen in (SLE) and could be the presenting manifestations of SLE in many patients. Also, it could mimic many primary hematological disorders.

The most common forms of hematologic manifestations in patients with SLE are anemia, leukopenia, thrombocytopenia, and the antiphospholipid syndrome (APS). Further details about APS and thrombosis are found in Chap. 12 (Thrombosis in Rheumatological diseases).

In this chapter; an overview of the hematologic manifestations of SLE will be discussed, with an algorithm at the end constructing a simple approach to hematological manifestations in SLE patients (Fig. 13.3).

13.4.1.1 Anemia

Many patients with SLE may have anemia at some point of time; the most common types of anemia in such patients are anemia of chronic disease, IDA, autoimmune hemolytic anemia (AIHA), drug-induced myelosuppression, and anemia associated with chronic renal failure which is uncommon [34]. There are different mechanisms which may explain the development of anemia in patients with SLE; at the end of this chapter, you will find a simple approach regarding common differential diagnosis, causes, and investigations. Figure 13.4 shows an algorithmic approach for Anemia in SLE patients.

Anemia of Chronic Disease

In a single-center prospective study of 132 SLE patients with anemia, ACD found as the most common type, representing 37% of all patients [34]. ACD is classified as normocytic and normochromic anemia and may be associated with a low reticulocyte count and a low serum iron, ; however bone marrow iron stores are adequate, and ferritin concentration is usually high.

Fig. 13.3 Algorithmic approach for anemia in SLE patients. In this approach the authors classified the anemia according to MCV and MCH, aiming to widen the differential diagnosis and to include non-rheumatological causes, life-threatening causes, and co-factors. The evidence to support this approach is based on cumulative lit-

erature, current guidelines, and the author's experience (Abbreviations: *HB* hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *LDH* lactate dehydrogenate, *-ve* negative, *+ve* positive, *IDA* iron deficiency anemia, *AIHA* autoimmune hemolytic anemia, *TTP* thrombotic thrombocytopenic purpura, *2ry* secondary)

13.4.2 Treatment

Usually the treatment is not indicated unless the patient has symptomatic anemia or renal impairment.

Patients with symptomatic anemia secondary to ACD and with no indication for corticosteroid or other immunosuppressant agents may be offered a therapy to enhance erythropoiesis, e.g., epoetin alfa (recombinant human erythropoietin). It should be started at 80 to 120 units/kg per week (usually as 2 to 3 injections per week). The patient should be reassessed after one month,

and the dose should be increased monthly until the hemoglobin level is maintained at ≥ 11 g/dL.

Darbepoetin alfa; a unique molecule that stimulates erythropoiesis with a longer half-life than recombinant human erythropoietin. A typical dose of darbepoetin alfa for adults is 0.45 mcg/kg once a week.

Erythropoietin was evaluated in patients with SLE and ACD; it was found that 58% of patients in one study had an adequate response to erythropoietin supplementation [35].

Patients with symptomatic anemia secondary to ACD who had insufficient response to erythro-

Fig. 13.4 Algorithmic approach for hematological manifestations of systemic lupus erythematosus (SLE). Classified by the affected component of the blood (platelets, HB, or WBC), in this approach, the authors suggest to broaden the differential diagnosis and to rule out non-rheumatological causes of mentioned abnormalities, including systemic diseases, infections, and drug-induced and primary hematological diseases. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience (Abbreviations: RA rheumatoid arthritis, R/O rule out,

HCV hepatitis C virus, HIV human immunodeficiency virus, TSH thyroid stimulating hormone, PT prothrombin time, PTT partial thromboplastin time, INR international normalization ratio, DIC disseminated intravascular coagulation, HIT heparin-induced thrombocytopenia, ITP immune thrombocytopenic purpura, TTP thrombotic thrombocytopenic purpura, MAHA microangiopathic hemolytic anemia, H. pylori *Helicobacter pylori*, WBC white blood cell, HB hemoglobin, Plt platelets, 2ry secondary, -ve negative, +ve positive, BM bone marrow, MDS myelodysplastic syndrome)

poietin supplementation, often improve on glucocorticoids at high doses (1 mg/kg/day) which is usually the next step in their management.

After 1 month of being on steroid, if the response is insufficient (e.g., hemoglobin still <11 g/dL), glucocorticoids dose should be tapered down rapidly and stopped.

If there is a response, the dose should be tapered as rapidly as to the lowest dose that maintains the improvement.

13.4.2.1 Iron Deficiency Anemia (IDA)

IDA is the second most prevalent type of anemia in patients with SLE [36]; in female, it could be secondary to menorrhagia, or it may

represent an acute or chronic blood loss from gastrointestinal tract usually as a result of chronic administration of NSAIDs and corticosteroids. It can exacerbate and/or coexist with ACD.

Long-standing anemia of chronic inflammation can also result in IDA.

Diffused pulmonary hemorrhage is an uncommon cause of anemia in patients with SLE.

13.4.2.2 Autoimmune Hemolytic Anemia (AIHA)

AIHA is an antibody-mediated erythrocyte destruction, and it may found in 5% to 14% of SLE patients [35].

(AIHA) is characterized by:

- High reticulocyte count,
- Reduced haptoglobin levels,
- High indirect bilirubin concentration,
- Positive direct Coombs' test,
- Found in up to 10% of SLE patients [37, 38].

Approximately 2/3 of patients with SLE-associated AIHA have symptoms at the onset of SLE [26]. The presence of hemolytic anemia could be associated with other severe SLE features including lupus nephritis, neuropsychiatric manifestations, and serositis. Some patients may have a positive Coombs' test without evidence of hemolysis. [36, 37]. The antibodies are divided into IgG-mediated "warm," and IgM-mediated "cold" agglutinin.

Treatment: AIHA usually improves on corticosteroids (1 mg/kg/day of prednisone) in 75 to 96% of patients [39].

Once the hematocrit starts to increase and the reticulocyte count decreases, prednisone can be quickly tapered down.

If the patient didn't achieve response, pulse steroid can be considered (e.g., 1 g methylprednisolone intravenously daily for 3 days) [39], azathioprine (up to 2 mg/kg per day) [40], cyclophosphamide (up to 2 mg/kg) [40], or splenectomy [41, 42].

Response rates for splenectomy in AIHA can reach up to 60% [41], ; however, other study has contradictory result [30]. In case of refractory AIHA, one can consider intravenous immune globulin [30], danazol (in doses of 600 to 800 mg/day) [42], mycophenolate mofetil [44], and rituximab [45].

Anemia due to chronic kidney disease:

An inappropriately low level of erythropoietin is the major feature of anemia due to chronic kidney disease. In this setting, typically decreased production of erythropoietin by the impaired kidneys plays a major role in the pathogenesis of this type of anemia. In such patients, specially patients with no other evidence of inflammation, prescribing erythropoiesis-stimulating agents

could be indicated in symptomatic anemia or if the hemoglobin is less than 11 g/dL.

13.4.2.3 Red Cell Aplasia

In SLE, red cell aplasia may occur secondary to antibody-mediated injury to erythropoietin or erythroblast in the bone marrow, although it is uncommon, but it has been reported [46, 47]. This type of anemia usually improves on corticosteroid, ; in refractory cases cyclophosphamide and cyclosporine have been successfully used.

13.4.2.4 Microangiopathic Hemolytic Anemia (MAHA)

SLE is one of many causes of thrombotic microangiopathic hemolytic anemia [48]. It usually presents with schistocytes in peripheral blood smear and high serum lactate dehydrogenase (LDH) levels as well as high indirect bilirubin concentration.

As you will see in the algorithm at the end of this chapter, it is essential to consider MAHA in any SLE patient who present with normocytic normochromic anemia, MAHA is manifested by schistocytes in peripheral film which necessitate urgent treatment with plasmapheresis and corticosteroid .

Thrombotic thrombocytopenic purpura (TTP), which is life-threatening condition, is typically manifested by a pentad of thrombocytopenia, fever, microangiopathic hemolytic anemia (MAHA), neurologic manifestations, and renal impairment.

Other patients with MAHA may not manifest with fever or neurologic abnormalities, presenting a condition called hemolytic-uremic syndrome (HUS). The pathogenesis of this syndrome isn't entirely known [49].

Treatment: In MAHA and TTP, plasmapheresis is considered the most important acute intervention. Because of the adverse outcome which associated with delay in its initiation, it should be started immediately in all patients with suspected TTP [50, 51].

In a review study, 28 patients with TTP managed with plasmapheresis, glucocorticoids alone,

or no therapy. The mortality rate was 25% in those treated with plasmapheresis, 50% in glucocorticoids alone group, and 100% in those who received no therapy [53].

The current recommendations suggest that plasma exchange should be immediately in the patients diagnosed to have TTP; it should be carried on at least for 5 days, along with pulse steroid (methylprednisolone 1 g intravenously daily for 3 days) with the first dose usually given immediately after the first plasmapheresis session [50]. Recently, in some cases of TTP anti-CD20 antibody, rituximab has been used, however more data are needed [52].

TTP-HUS is often associated with reduced activity of ADAMTS13 (<10%), usually due to an inhibitor of ADAMTS13 activity. However, results of ADAMTS13 activity measurement should not influence the decision to initiate plasma exchange, and plasmapheresis shouldn't be delayed while awaiting its result [50, 53].

13.4.3 WBC Abnormalities

At the end of this chapter, the reader will find an algorithm which constructing an approach to SLE patients who present with WBC abnormalities; including leukocytosis, leucopenia, neutropenia, lymphocytopenia, and other abnormalities. This approach emphasizes rolling out serious conditions as well as considering SLE related WBC disorders.

13.4.3.1 Leucopenia and Neutropenia

Leucopenia is a characteristic feature of SLE and can include lymphopenia, neutropenia, or both. It defined as less than 4000 cells/mL of white blood cell (WBC) count, and it usually represents an active disease. According to the American College of Rheumatology (ACR, leucopenia is considered as one of the criteria to diagnose SLE [54]. It can be seen in up to 50% to 60% of SLE patients [55, 56].

Other comparative retrospective study which was done in Saudi Arabia showed that the most common hematologic presentation among SLE patients was leucopenia which was found in 58.7% of the patients [57].

In some cases, leukopenia becomes challenging specially if the patients require a medication that can cause bone marrow suppression, e.g., cyclophosphamide, azathioprine, methotrexate, and, rarely, cyclosporine, mycophenolate mofetil, or HCQ. If a patient developed a rapid leucopenia, hemophagocytic syndrome should be considered, and proper workup should be perused [55].

Neutropenia may reflect primary hematological disease, infection, or treatment side effects (e.g., cyclophosphamide or azathioprine); however, all those causes should be considered in correlation with history and clinical finding. In SLE, neutropenia which attributed to an active disease usually respond to steroids.

13.4.3.2 Lymphocytopenia

Lymphopenia is considered one of the most prevalent hematological features of SLE, and although it was noted to be contributory to leucopenia, yet it can be independent to total white blood cell count. Reduced absolute lymphocytic count can correlate with SLE activity, and those with absolute lymphocytic count less than 1500/ μ L at diagnosis may have a higher frequency of fever, musculoskeletal manifestations, and neuropsychiatric manifestations [55].

13.4.3.3 Decreased Eosinophils and Basophils

Generally, corticosteroids may contribute to a low absolute eosinophil and monocyte counts.

Basophil count can be reduced as well in SLE, especially during lupus flare, basophil degranulation usually occurs which result in the release of platelet activating factor and as well as other mediators which can play a role in vascular permeability and immune complex deposition [31].

13.4.3.4 Treatment of Leukopenia

Not all SLE patients with leucopenia need to be treated, unless the patient has neutropenia with recurrent infections. On other hand, side effects of the treatment may complicate the situations, ; prednisone (10 to 60 mg/day) may increase the leucocyte count but may result in high risk of

infections as well; immunosuppressive therapies like azathioprine or cyclophosphamide may contribute toward the worsening of the leukopenia through their effect on bone marrow suppression [31]. In such cases, these medications should be used with caution and frequent monitoring of white blood cell count and for signs of infections.

Treating leukopenia in SLE in other settings may result in unfavorable outcomes. As an example, recombinant granulocyte colony-stimulating factor (G-CSF) studied in the treatment of severe neutropenia associated with refractory infections, although it was effective in increasing neutrophilic count, yet it was associated SLE flare in three out of the nine patients in this study [32].

13.4.3.5 Leukocytosis

Leukocytosis can be found in patients with SLE. Two contributing factors include underlying infectious process or leukocytosis associated with high dose of steroids [31]. It also can be found during SLE flare. In case of leukocytosis secondary to infections, shifting of granulocytes to more immature forms (a left shift) is usually seen.

13.4.4 Platelet Abnormalities

Both qualitative and quantitative disorders of platelets are not uncommon in SLE patients; at the end of this chapter, you will find a simple approach to platelets disorders, considering the life-threatening conditions, disease activity, and other associated diseases. It has been found that almost in 25% to 50% of SLE patients may have a mild thrombocytopenia with platelet counts ranging between 100,000 and 150,000/microL, and 10% of SLE patients may have more severe form in which the counts become less than 50,000/microL [1].

In a cohort study of 632 patients with SLE, the percentage of patients with platelet counts ranging between 50,000 to 100,000/ μ L was 54%, while those with counts between 20,000 and 50,000/ μ L represent 18%, and patients with counts less than 20,000/ μ L represent 28% of the cohort [58].

There are many potential causes of thrombocytopenia in SLE patients. Among them, immune-mediated platelet destruction is considered the most common cause, but platelet consumption is another factor specially in association with MAHA or may be due to reduced platelet production secondary to cytotoxic medications.

Pathogenesis—the main mechanism is binding of immunoglobulin to the surface of the platelets which later get involved in the phagocytosis inside the spleen, similar to idiopathic thrombocytopenic purpura (ITP) [51]. Another mechanism in some patients involves bone marrow suppression by cytotoxic medications, increased consumption due to a thrombotic microangiopathy (e.g., TTP), the antiphospholipid syndrome, or antibodies against the thrombopoietin receptor on megakaryocytes or their precursors.

Patients with SLE can present initially with ITP followed by other manifestations later on.

In patients with isolated ITP, it has been found that 3–15% may develop SLE [59]. Evans syndrome, which is defined as the presence of both autoimmune thrombocytopenia and autoimmune hemolytic anemia, can also precede the onset of SLE.

Thrombocytopenia is uncommonly severe, and complications related to bleeding are generally low as a minority of patients only experiences severe bleeding. However, it is well-known that thrombocytopenia in patients with SLE considered poor prognostic factor and put the patient at risk of other organ involvement such as cardiac involvement, nephritis, or neuropsychiatric manifestation [38, 48].

Our algorithm at the end of this chapter simplified the approach to thrombocytopenia in SLE patients; we suggest to do peripheral blood smear to rule out serious conditions such as MAHA, TTP, and malignancies; to order lupus anticoagulant and anticardiolipin to rule out APS; to do hemolysis workup and direct Coombs' test to rule out AIHA and Evans syndrome; and to consider disease activity as well as secondary thrombocytopenia causes in your differential diagnosis.

Treatment: In patients with thrombocytopenia with counts ranging between 20,000/microL and 50,000/microL, usually they have prolonged

bleeding time; however bleeding is rarely seen with this range, while counts of less than 20, 000/microL can be associated with petechiae, purpura, ecchymoses, epistaxis, gingival, and other clinical bleeding. Treatment is usually indicated for patients with symptoms and counts of less than 50, 000/microL and for those with counts of less than 20, 000/microL. Glucocorticoid therapy is the main treatment, prednisone (1 mg/kg per day in divided doses) [47]. Dexamethasone also can be used as 40 mg/day dose for 4 days, with repeating the doses every 2–4 weeks, an intervals of 2–4 weeks may have similar remission rates and better long-term responses than those treated with daily prednisone [39]. The majority of patients improve on glucocorticoid within 1–8 weeks; in case of no response within 1–3 weeks or intolerance to steroids, other lines of therapy should be considered. The choice of second medication depends on the severity of the thrombocytopenia and the presence of other SLE manifestations.

- **Azathioprine** (0.5 to 2 mg/kg per day) [60].
- **Cyclophosphamide**, given as daily oral doses or intravenous pulse therapy. Intravenous pulse cyclophosphamide is usually preferred in patients with concurrent active lupus nephritis [40].
- **Intravenous immune globulin**, which is an effective and usually considered a first choice in conditions when a quick increase in platelets is needed, e.g., active bleeding or in case of emergency surgery [43].
- **Mycophenolate mofetil**, usually considered in patients who failed other medications [41].
- **Rituximab**—It is a chimeric monoclonal antibody which has been used as well to treat primary ITP (without SLE) refractory to previously mentioned therapies. It is given as once weekly dose for 4 consecutive weeks at doses of 375 mg/m² [42].
- **Splenectomy**—Splenectomy may increase the platelet count, but it does not reliably make a consistent remission of thrombocytopenia. After splenectomy, relapse may happen and has been reported at varying times from 1 to 54 months following surgery.
- **Thrombocytopenia following splenectomy**—Some patients may have persistent thrombocytopenia following splenectomy; those patients may respond to azathioprine, cyclophosphamide, rituximab, intravenous immunoglobulin, or danazol [44]. Patient who underwent splenectomy is at high risk of pneumococcal infections; that's why it is highly recommended for patients to receive immunization with pneumococcal vaccine before splenectomy if possible.
- **Danazol** (400 to 800 mg/day) [45]—May be considered for patients who failed other therapies. In a series of 34 patients, excellent long-term results were achieved with danazol [46].
- **Vincristine**—Successful use of vincristine has been reported [46].

13.4.4.1 Thrombocytosis

Thrombocytosis is unfrequently seen in patients with SLE.

We suggest to ruling out secondary causes such as infection or other inflammatory process, or APS.

As an example, among 465 patients with SLE, 17 (3.7%) were found to have thrombocytosis (platelet $\geq 400,000/\text{mm}^3$). Three of these patients had one or more of the following features on peripheral blood film: Howell-Jolly bodies, spherocytes, and target cells.

Ultrasound, CT, and liver-spleen scintigraphy failed to demonstrate a spleen. All three patients had aPL [69]. These observations suggest that autosplenectomy may occur in patients with SLE, perhaps mediated by aPL.

13.4.5 Pancytopenia

Destruction of all three cell line (red blood cells, white blood cells, and platelets) may occur peripherally; it also may suggest bone marrow failure, as in the case in aplastic anemia. Hence, bone marrow biopsy is the most significant diagnostic test to do. In a study published in 2012, concluded that among SLE patients with peripheral cytopenia, the incidence of bone marrow

abnormalities is high. Bone marrow may be one of the common affected organs by immune dysregulation in active SLE. Peripheral cytopenia can be consequently improved after treatment of disease activity; hence, bone marrow biopsy should be recommended in patients with refractory cytopenia to conventional treatment [61].

There are many causes of bone marrow failure which include drugs and coexisting diseases such as acute leukemias, myelodysplastic syndromes, severe megaloblastic anemia, paroxysmal nocturnal hemoglobinuria (PNH), and infections. Furthermore, unexplained cytopenia can be associated with bone marrow necrosis, dysplasia, and distortion of the bone marrow architecture [62, 63].

13.4.6 Lymphadenopathy and Splenomegaly

Patients with SLE may present with lymphadenopathy, which could be regional or peripheral lymphadenopathy. The common sites involved in SLE lymphadenopathy are cervical and axillary nodes. In a cohort of 698 patients with SLE, lymphadenopathy was found in 59% of the study group. Patients who presented with lymphadenopathy as initial presentation represented 1% of the cohort. Furthermore, the lymph nodes' size ranged from 3 to 4 centimeter in diameter, most of them were not tender and soft. [64].

The typical histological finding in SLE lymphadenopathy includes reactive lymphoid follicular hyperplasia with variable levels of coagulative necrosis. A usual finding, yet highly associated with SLE, is the presence of hematoxylin bodies [1].

SLE lymphadenopathy is present usually initially at the diagnosis and during SLE flares in most of the cases. When SLE patient presents with an enlarged lymph node, other etiologies should be considered such as infection and lymphoproliferative disorders (e.g., angioimmunoblastic T-cell lymphoma); both of these diseases are relatively common in SLE compared to normal population. In case of infectious lymphadenopathy, lymph nodes are usually tender.

Splenomegaly may present in 10–46% of SLE patients, especially during SLE flares, and it should not necessarily be linked to cytopenia.

Based on the fact that splenomegaly and lymphadenopathy are common among SLE patients, physicians should consider lymphoproliferative disorders in those patients, especially because patients with SLE have up to fivefold higher risk of non-Hodgkin lymphoma [65].

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a disease characterized by the presence of fever, lymphadenopathy commonly in cervical nodes, and constitutional symptoms [67].

KFD is usually self-limited, and sometimes confused with SLE or lymphoma. Typically, it is present in young women, and preceded by flu-like illness. The etiology of KFD remains unknown. No specific laboratory tests are associated with this disease, ; however, 50% of the patients may develop mild leucopenia. Histological finding of hematoxylin bodies and plasma cells and the DNA deposition in the blood vessels are highly associated with SLE lymphadenitis and help differentiating between the two diseases. It is always recommended to exclude SLE with proper serological testing before making the diagnosis of KFD. There have been few reports of SLE with coexisting KFD [55, 64, 66].

Castleman disease, also known as angiofollicular lymph node hyperplasia, is one of the rare lymphoproliferative diseases which manifested as enlarged lymph node that may or may not be associated with constitutional symptoms and could be confused with SLE or lymphoma. Its etiology remains unknown.

13.4.7 Antibodies to Clotting Factor and Phospholipids

Hematologic manifestations of SLE may involve coagulation system in some patients. SLE patients may have antibodies directed against the following factors VIII, IX, XI, XII, and XIII [1].

These antibodies can cause a biochemical abnormality (in vitro), but it also can cause

some clinical abnormalities manifested as overt bleeding.

Antiphospholipid antibodies (aPL) are commonly seen in SLE patients. They can cause a prolonged partial thromboplastin time through lupus anticoagulant activity. Clinically, these antibodies have well-recognized risks of arterial as well as venous thrombosis and thrombocytopenia. Additionally, female in childbearing age with aPL is at high risk fetal loss [68].

Moderate to high titers of aPL and other antibodies to binding proteins such anticardiolipin antibodies can be associated with certain clinical features. If aPL is present with certain clinical features, it may suggest the presence of antiphospholipid syndrome (APS) (see Chap. 12, , Thrombosis in Rheumatological diseases).

High prevalence of aPL in SLE patients following treatment with cyclophosphamide was noted in a single retrospective study that compared 177 cyclophosphamide-treated SLE patients to 203 patients with SLE never treated with this alkylating agent [52]. Sero-conversion occurred at a higher rate in the cyclophosphamide-treated patients (19 versus 1%, respectively).

13.5 Macrophage Activation Syndrome (MAS)

13.5.1 Introduction

The macrophage activation syndrome (MAS), also known as hemophagocytic lymphohistiocytosis (HLH), is a condition that requires urgent attention and treatment. It is classically associated with systemic juvenile idiopathic arthritis in children and adult onset Still's disease [69], but can occur in any rheumatic disease including SLE, RA, vasculitis, Sjögren's syndrome, mixed connective tissue disease, systemic sclerosis, and inflammatory myopathies [70]. MAS can develop anytime during rheumatologic disease. It can be the first manifestation of the rheumatologic disease or may occur while patient is on treatment. It may also be associated with infection.

Hematological manifestation of MAS includes pancytopenia, hepatosplenomegaly, hyperferritinemia, and coagulopathy.

An overview of MAS is presented here, with an algorithm at the end constructing a simple approach to diagnose MAS/HLH in a patient with rheumatologic disorder.

13.5.1.1 Pancytopenia

Together, anemia and thrombocytopenia are present in more than 80% of patients [71–73]. The median hemoglobin level is 7.2 g/dl, and platelet count is 69, 000/microL [71]. Neutropenia with absolute counts below 1000/microL is not uncommon.

Patients with juvenile idiopathic arthritis and adult onset Still's disease may develop cytopenia later in the course of disease as they tend to have elevated blood counts prior developing MAS.

13.5.1.2 Hepatosplenomegaly

Reticuloendothelial system is commonly affected in MAS/HLH. In retrospective study including 249 patients of HLH, hepatomegaly was observed in 95% and lymphadenopathy in 33% of the patients. Another European registry includes 122 patients, 97% of them were found to have splenomegaly [74].

13.5.1.3 Hyperferritinemia

Severe hyperferritinemia is associated with MAS/HLH; a level above 10, 000 ng/mL is 90% sensitive and 96% specific for MAS/HLH [75].

In HLH-94 study, it was found that ferritin greater than 10,000, 5000, and 500 ng/mL were seen in 25, 42, and 93%, respectively [72]. It is very rare to have MAS/HLH with ferritin levels below 500, ; however, low ferritin does not totally exclude MAS.

13.5.1.4 Coagulopathy

High partial thrombin time and high prothrombin time due to liver involvement and impaired liver synthetic function in association with disseminated intravascular coagulopathy are seen in MAS/HLH [70].

Fig. 13.5 Algorithmic approach for hyperferritinemia with pancytopenia in rheumatologic diseases patients. This approach is based on ferritin level; the authors suggest to broaden the differential diagnosis and to rule out disease activity and non-rheumatological causes, including systemic diseases, infections, and drug-induced and

primary hematological diseases. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience. (Abbreviations: *R/O* rule out, *MAS* macrophage activation syndrome, *HLH* hemophagocytic lymphohistiocytosis)

The HLH-2004 revised diagnostic criteria are used to diagnose MAS/HLH. Five out of the eight criteria as shown in Fig. 13.5 are required for the diagnosis.

13.5.2 Treatment

Salvage treatment for adults with refractory/relapsing HLH usually requires intensification using combined chemotherapy and consolidation with allogeneic stem cell transplantation. Novel agents are providing promising therapeutic alternatives including those incorporating ruxolitinib (JAK1/2 inhibitor), anakinra (IL-1 blockade), alemtuzumab, and emapalumab [76].

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