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Lessons Learned from Bone Marrow Failure in Systemic Lupus Erythematosus: Case Reports and Review of the Literature

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aplastic anemia; autoimmune myelofibrosis; bone marrow failure; paroxysmal nocturnal hemoglobinuria; systemic lupus erythematosus

1.1 Introduction

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease with variable multisystem involvement. Hematologic abnormalities involving multiple cell lineages are common in SLE. Lymphopenia was present in 75% among a large cohort of SLE patients and occurred more frequently than any other criterion used to classify the disease.[1] Anemia is estimated to occur in about 50% of patients.[2] While anemia of chronic disease and iron deficiency are quite common, autoantibody- or complement-mediated autoimmune hemolytic anemia are occasionally encountered.[3] Autoimmune thrombocytopenia can result in severe thrombocytopenia and bleeding diatheses. Another less common cause of thrombocytopenia is thrombotic microangiopathy, a complication that also leads to a Coombs' negative hemolytic anemia owing to microvascular thrombosis.[4] Finally, neutrophil abnormalities may include neutropenia, excessive NETosis, and the appearance in the peripheral blood of a population of low density granulocytes.[5]

Whereas cytopenias in SLE are typically secondary to peripheral destruction, acquired bone marrow failure is a rarely reported mechanism of cytopenias in SLE. Myelodysplastic syndrome,[6] aplastic anemia (AA),[7] paroxysmal nocturnal hemoglobinuria (PNH),[8] autoimmune myelofibrosis (AIMF),[9] pure red cell aplasia[10] and hemophagocytosis[11] have all been described in SLE. Therefore, it is essential to determine the cause of the hematologic abnormality in the patient with SLE as treatments may vary dependent upon the underlying pathology.

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In this review, we present two cases of AIMF in SLE as well as two cases of AA, one with features of PNH. We conducted a review of the current literature with the goal of more clearly characterizing cases of AIMF, AA and PNH associated with SLE. Specifically, we collected information regarding SLE serologies, hematologic manifestations, bone marrow findings, treatment, and outcomes. We discuss current theories on the pathophysiology of AIMF, AA and PNH in SLE and the challenge inherent in differentiating them from primary hematological disorders. We suggest diagnostic and therapeutic strategies for these disorders in SLE based on lessons learned from the present and previous cases.

2.1 Case Reports

2.1.1 Autoimmune myelofibrosis

A 69-year-old female with SLE consisting of arthritis presented with lethargy and both a malar and discoid rash on exam. She was not receiving any therapy at the time of admission. Leukocyte count was 2.3×10^9/l with lymphopenia (0.4×10^9/l), hemoglobin was 8.6 g/dl, and platelets were 19×10^9/l. Reticulocyte index was 0.3. Anti-nuclear antibody titer was 1:1280; anti-double stranded DNA antibody was 234 IU/ml (normal < 30 IU/ml); anti-Smith was negative. C3 and C4 were 17.4 mg/dL (88–252 mg/dL) and 4.6 mg/dL (13–75 mg/dL), respectively. Direct Coombs' test was negative. Computed tomography did not reveal splenomegaly. A bone marrow biopsy revealed reticulin fibrosis with plasmacytosis (Figure 1). A diagnosis of AIMF was made. High dose steroids were given without improvement in thrombocytopenia. Intravenous immunoglobulin (IVIG) was given for 5 days with gradual improvement. However, 3 days after completion of IVIG, the hemoglobin dropped to 6.6 g/dl. Initially negative 18 days prior, the direct Coombs' test was positive for immunoglobulin G, and elution yielded anti-A and anti-B antibodies. Immune-mediated hemolysis secondary to IVIG was diagnosed, and her anemia stabilized with transfusions. One month later, all counts were normal.

2.1.2 Autoimmune myelofibrosis

A 55-year-old African American female with SLE previously consisting of arthritis and nephritis on mycophenolate mofetil (MMF) presented with severe lethargy but no significant findings on exam. Leukocyte count was 3.3×10^9/l with lymphopenia (900/uL), hemoglobin was 7.3 g/dl, and platelets were 23×10^9/l. Reticulocyte index was 0.7, and there was no evidence of hemolytic anemia. Anti-nuclear antibody titer was 1:2560; anti-double stranded DNA antibody was 213 IU/ml. C3 and C4 were 49 mg/dL and 14.1 mg/dL, respectively. Computed tomography did not reveal splenomegaly. MMF was discontinued, and high dose steroids were administered. However, there was no improvement in pancytopenia. A bone marrow biopsy revealed reticulin fibrosis with plasmacytosis. IVIG was given without improvement. Labs were also notable for undetectable fibrinogen, with elevated D-dimer and international normalized ratio, suggestive of disseminated intravascular coagulation. The patient expired shortly thereafter.

2.1.3 Aplastic anemia

A 67-year-old Asian female presented with 3 weeks of epistaxis, fatigue, dyspnea on exertion and dizziness, with ecchymosis on exam. Leukocyte count was 3.3×10^9/l with

neutropenia (820/uL), hemoglobin was 6.3 g/dl, and platelets were 4×10^9/l. Reticulocyte index was 0.2, and there was no evidence of hemolytic anemia. Anti-nuclear antibody titer was 1:640; anti-double stranded DNA antibody was 74 IU/ml, while anti-Smith was negative. C3 and C4 were 68.1 mg/dL and 20.1 mg/dL, respectively. Computed tomography did not reveal splenomegaly. A bone marrow biopsy revealed marked hypocellularity, but no cellular atypia. A diagnosis of aplastic anemia was made. High dose steroids and intravenous cyclophosphamide were given; however, repeat bone marrow biopsy revealed persistent hypocellularity. She was then given antithymocyte globulin for 5 days, and cyclosporine was started. She had only a partial response (leukocyte count unchanged; hemoglobin (8.7 g/dL) and thrombocytopenia (34×10^9/l) improved but still transfusion dependent), and therefore therapy with eltrombopag was initiated.

2.1.4 Aplastic anemia and PNH

A 70-year-old Indian female presented with gingival bleeding and a petechial rash. Leukocyte count was 2.4×10^9/l with lymphopenia (800/uL) and neutropenia (660/uL); hemoglobin was 8.9 g/dl, and platelets were 2×10^9/l. Reticulocyte index was 0.5. Lactate dehydrogenase was 226 (135–225 U/L), haptoglobin was undetectable, and direct Coombs' test was positive for immunoglobulin G with elution revealing a panagglutinin. Anti-nuclear antibody titer was 1:1280; anti-double stranded DNA antibody was 162 IU/ml, while anti-Smith was negative. Complement levels were normal. The dilute Russell's viper venom time prolongation was felt to represent a lupus anticoagulant. Computed tomography did not reveal splenomegaly. An initial bone marrow biopsy revealed polyclonal B lymphocytosis and plasmacytosis, and a second biopsy 12 weeks later also revealed hypocellularity (Figure 2). She was given high dose steroids, IVIG, and intravenous rituximab without improvement. Peripheral blood flow cytometry revealed a significant paroxysmal nocturnal hemoglobinuria phenotype of red blood cells (CD59 deficient), granulocytes (CD16, CD24 deficient and aerolysin positive), and monocytes (CD14 deficient). Therapy with antithymocyte globulin and cyclosporine was initiated. The patient remained transfusion-dependent, and a peripheral smear now revealed 3–4 schistocytes per high power field. Plasma exchange, which was initiated for concern of cyclosporine-induced thrombotic thrombocytopenic purpura, resulted in improvement in hemolysis. Peripheral blood flow cytometry revealed an increase in the PNH clone in granulocytes and monocytes, which was much greater than the clone of PNH red blood cells. This in combination with elevated serum LDH (607 U/L) and undetectable haptoglobin suggested ongoing hemolysis, and eculizumab treatment was initiated.

3.1 Review of Published Cases

3.1.1 Method

Using PubMed, a Boolean search of the literature was performed by crossing the keywords "systemic lupus erythematosus," AND ["bone marrow fibrosis" or "bone marrow failure" or "myelofibrosis" or "aplastic anemia" or "paroxysmal nocturnal hemoglobinuria"]. We also examined additional references from the articles we obtained from this method. The articles were written between 1969 and 2016. Only papers written in English were reviewed.

3.1.2 Autoimmune Myelofibrosis (33 cases)

Patient demographics (Table 1)—29 were female, and 4 were male. The age range was 12 to 70 years, with a mean age of 37.

Peripheral hematologic abnormalities (Table 1)—Anemia (hemoglobin < 10 grams/dL) was present in 28/33, leukopenia (WBCs < 4.5×10^9/L) in 24/33, and thrombocytopenia (platelets < 150×10^9/L) in 30/33. Lymphopenia (lymphocytes < 1×10^9/L) was present in 8/13 (20 missing data), while neutropenia (neutrophils < 1.5×10^9/L) occurred in 11/16 (17 missing data). Hemolysis was suggested by an elevated reticulocyte index in 2/15 (18 missing data), the combination of a high LDH and low haptoglobin in 2/11 (22 missing data), and a low haptoglobin alone in 1/11. A DAT test was positive in 12/24 (9 missing data). On the peripheral smear, leukoerythroblastosis was present in 8/15 (18 missing data), and tear drop cells were seen in 7/15, findings characteristic of primary myelofibrosis.

Immunological findings (Table 1)—Antinuclear antibodies and hypocomplementia were present in all patients, double-stranded DNA (dsDNA) in 18/30 (3 missing data), antiphospholipid antibodies (anticardiolipin, beta-2 glycoprotein or the lupus anticoagulant) in 4/33, anti-SSA in 3/33, and antihistone and ribonucleoprotein (RNP) antibodies in 1/33 each.

Bone marrow findings (Table 4)—All bone marrow biopsies reported either myelofibrosis/myelosclerosis, increased reticulin, increased fibroblasts, or fibrosis.

Treatment and outcomes (Table 4)—Corticosteroids were universally used; 17/33 improved with corticosteroids alone, 5/33 received IVIG with 4 improving, 1/33 received hydroxychloroquine without improvement, 1/33 received cyclophosphamide with improvement, 2/33 received cyclosporine with 1 improving, 3/33 received azathioprine with improvement, 1/33 received a combination of vincristine and colchicine with improvement, and 1/33 received plasma exchange without improvement.

3.1.3 Aplastic Anemia (27 cases)

Patient demographics (Table 2)—25 were female, and 2 were male. The age range was 6 to 74 years, with a mean age of 32.

Peripheral hematologic abnormalities (Table 2)—Pancytopenia occurred in 20 cases (7 missing data). Lymphopenia was present in 9/13 (14 missing data), and neutropenia in 15/18 (9 missing data). Hemolysis occurred in 1/27, as evidenced by a high LDH and undetectable haptoglobin in association with a positive direct antiglobulin (DAT) result. In this case, a low reticulocyte index and neutropenia suggested concurrent bone marrow insufficiency. Flow cytometry was negative for a PNH clone in this case. A DAT test was positive in 5/17 (10 missing data).

Immunological findings (Table 2)—Antinuclear antibodies were found in all patients, dsDNA antibodies in 20/24 (3 missing data), hypocomplementia in 15/27, antiphospholipid

antibodies in 4/27, anti-SSA antibodies in 4/27, anti-Smith antibodies in 2/27, anti-RNP antibodies in 1/27, and anti-histone antibodies in 1/27. Inhibitors of bone marrow precursor cells in SLE sera were found in 6/12 (50%) cases tested.

Bone marrow findings (Table 5)—All bone marrow biopsies reported either hypocellularity or aplasia.

Treatment and outcomes (Table 5)—9/27 received cyclosporine (2 improved with therapy alone, 1 with antithymocyte, and 1 with antithymocyte and hydroxychloroquine), 6/27 received corticosteroids alone with 5 improving, 6/27 received plasma exchange/plasmapheresis (3 improved with therapy alone, 1 with cyclophosphamide, and 1 with corticosteroids), 6/27 received cyclophosphamide (1 improved with therapy alone, 2 with corticosteroids, and 1 with plasma exchange), 3/27 received androgens with 2 improving (1 with corticosteroids), 2/27 received rituximab with 1 improving, and 1/27 received hydroxychloroquine alone with improvement. Of note, of the 6 cases of AA in which a serum inhibitor was found, 5 cases were treated with plasma exchange resulting in complete recovery. The remaining case was treated with cyclophosphamide and recovered.

3.1.4 Paroxysmal Nocturnal Hemoglobinuria (4 cases)

Patient demographics (Table 3)—All cases were female. The age range was 29 to 70 years, with a mean of 47 and a median of 28.

Peripheral hematologic abnormalities (Table 3)—Pancytopenia occurred in 1/3 (1 missing data). Leukopenia was present in 2/3 (1 missing data), anemia in 2/3 (1 missing data), and thrombocytopenia was present in all cases. Lymphopenia and neutropenia were present in our case, while other cases did not report these values. Hemolysis, as evidenced by a combination of high LDH and low haptoglobin, was present in 3/4 cases. A DAT was positive in our case. Flow cytometry confirmed the diagnosis of PNH in all cases, while the Ham and sugar water tests were each used in 2/4 cases.

Immunological findings (Table 6)—Antinuclear antibodies were found in all patients and dsDNA antibodies in 3/4. Hypocomplementia, anti-SSA antibodies, and the lupus anticoagulant were each found in 1/4.

Bone marrow findings (Table 6)—Only our case had a bone marrow biopsy, which was ultimately consistent with concurrent AA.

Treatment and outcomes (Table 6)—Steroids were administered in 3/4 with 2 improving. The remaining case received supportive care only and improved. The patient described in our case remained transfusion-dependent despite AA treatment, and eculizumab was recently initiated for PNH.

4.1 Discussion

4.1.1 Pathophysiology of bone marrow failure in SLE

The attribution of bone marrow failure to SLE can be particularly difficult. There have been several theories posited regarding how SLE may contribute to AIMF, AA and PNH. First, myelofibrosis has been described as a clonal proliferation of myeloid stem cells accompanied by replacement of the bone marrow stroma with fibrous tissue. In SLE, circulating immune complexes and autoantibodies may act on megakaryocyte Fc-receptors and release growth factors, such as platelet-derived growth factor and transforming growth factor-β, which are both known to induce collagen production.[12,13] Complement system activation is part of SLE pathogenesis,[14] and may contribute to bone marrow failure. Activation of the alternative complement pathway has been described in SLE.[15] In a case series of myelofibrosis, activation of the alternative pathway of the complement system was reported in 4 patients, 2 of which had a positive ANA.[16] It is interesting to note that in all AIMF cases reviewed here where serology was reported, hypocomplementemia was universal (the case reported in Lau et al 1969 was before the assessment of complement as a measure of SLE disease activity was routinely done in clinical practice).[17] Despite these observations, no specific antibodies or biomarkers in SLE have confirmed pathologic associations with myelofibrosis.

The association of SLE with AA in terms of invoking an autoimmune mechanism is perhaps less controversial than with AIMF. There have been 6 instances where an inhibitor in SLE serum has been identified: in 3 cases, a complement-dependent IgG antibody; in 1 case, a non-complement-dependent IgG antibody; and in 2 other cases an inhibitor was not identified.[18–22] These complement or non-complement-dependent antibodies inhibit in vitro bone marrow colony formation from granulocyte-macrophage progenitor cells[18,19] and blast-forming units-erythroid.[19] Autoantibodies against various proteins, such as kinectin, moesin and diazepam-binding inhibitor-related protein have been described and may have a subsidiary role in the pathophysiology of AA.[23] In addition, apoptotic bodies have been discovered in the bone marrow of SLE patients, findings not present in normal bone marrow.[24] Whereas their significance is uncertain, delayed clearance of apoptotic debris leads to prolonged exposure of autoantigens and predisposes to antibody production. Other studies have failed to detect inhibiting antibodies, which suggests that other mechanisms are involved in the pathogenesis of AA. For example, T cell dysregulation may play a role. Cytokines such as IFNγ and TNFα are elevated in SLE and contribute to pathogenesis.[14] Secretion of IFNγ and TNFα by T cells suppresses proliferation of early and late hematopoietic progenitor and stem cells. These cytokines induce expression of Fas receptor on CD34 + progenitor cells, and triggering by Fas ligand initiates apoptosis.[7] A unique form of AA, pure red cell aplasia, has also been described in SLE and is characterized by severe normocytic anemia, reticulocytopenia, and an absence of erythroblasts from an otherwise normal marrow.[25] Similar to AA, a serum inhibitor is implicated in the majority of cases.[26,27] Antibodies against erythropoietin have been identified.[28] Also analogous to AA, suppression of erythropoiesis seems to be mediated by T lymphocytes in a subset of patients.[27,29]

The basic defect in PNH is a somatic mutation in the PIG-A gene that causes loss of the glycosylphosphatidylinositol (GPI) anchor proteins on blood cells. Loss of GPI proteins, namely the delay accelerating factor (DAF or CD55) and the membrane inhibitor of reactive lysis (MIRL or CD59) proteins, results in increased susceptibility to complement-mediated lysis of erythrocytes, leukocytes, and platelets. A deficiency of CD55 and CD59 on peripheral blood cells has been described in SLE patients without a diagnosis of PNH.[30,31] In SLE, excessive complement activation causes damage to tissue and autologous cells.[14] These could include bone marrow progenitor cells in the setting of CD55 and CD59 deficiency. It is interesting to note that PNH clones have been found in a large percentage of cases of bone marrow failure; in one large series, a clone was present in about 1/3 of 200 AA cases and 20% of approximately 100 myelodysplasia cases.[32] Furthermore, small clones are present in a large proportion of AA patients, and these clones may expand over time to cause clinically significant hemolysis.[33] It is not unreasonable to speculate that the development of PNH clones in a SLE patient may leave them more susceptible to complement-mediated hemolysis, given that SLE patients often have an activated complement system. Also of note, there is existing evidence that autoimmunity may play a role in PNH, as it does in AA. Previous reports have documented abnormalities in the T-cell repertoire in PNH, and recent evidence has shown the pathogenic role of a specific subset of cytotoxic T-cells.[34] Furthermore, evidence suggests that cells harboring a PIG-A mutation may escape this cytotoxic attack.[35] Therefore, the cytotoxic T-cells may allow a growth advantage to PNH clones in this disease.[33]

4.1.2 Diagnostic and therapeutic strategies

This review of AIMF, AA and PNH in the setting of SLE, as well as our own cases in which there was diagnostic confusion in regards to whether SLE was contributing to bone marrow failure, allows us to suggest some diagnostic and therapeutic strategies.

Autoimmune myelofibrosis may be more prevalent in SLE than the literature suggests. The first case of AIMF was described in 1984, and in 1993, there were 8 reported cases of AIMF in SLE. Herein, we reviewed 33 cases, demonstrating that the number of reported cases has risen significantly.[36,37] Furthermore, we reviewed 27 cases of AA, and in these cases the absence of reticulin fibrosis was not often specified. Therefore, the distinction between AIMF and AA in SLE is not always clear, and AIMF may thus be underreported. This observation emphasizes that one must have a heightened suspicion for AIMF in cases of pancytopenia in SLE, especially since pathologists do not routinely stain for reticulin. It is notable that some authors suggest that autoimmune disease such as SLE should be sought when myelofibrosis occurs in the absence of the JAK2 mutation.[38] This mutation has been found in up to 50% of those with primary myelofibrosis.[39] Bone marrow fibrosis in SLE usually responds to corticosteroids, as opposed to primary myelofibrosis. In non-responders to corticosteroids in AIMF, IVIG has been used in 4 previous cases, with 2 responding favorably.[9,38,40,41] Our case was unique in that AIMF did not respond to corticosteroids, yet IVIG was ultimately successful, despite the uncommon complication of immune-mediated hemolysis. Of note, plasma exchange has not been efficacious in AIMF.[9]

In contrast, plasma exchange has uniformly resulted in complete recovery from AA attributed to SLE when an inhibitor has been found in serum.[18–21] In these cases, SLE disease-phase serum suppressed the in vitro growth of progenitor cells from bone marrow of normal donors, confirming the presence of a serum inhibitor. The fact that an inhibitor was found in 50% of the 12 AA cases in which it was sought, coupled with complete recovery with plasma exchange, illustrates that plasma exchange is an effective therapeutic option in AA and SLE.

It is imperative to include PNH in the differential when pancytopenia presents in the setting of SLE, especially since aplastic anemia and PNH have close clinical and pathophysiological connections. The risk of developing PNH is approximately 15–25% in patients with acquired aplastic anemia.[42] At the initial diagnosis of aplastic anemia, more than 20% of patients display a small or moderate GPI-deficient clonal population in the bone marrow.[43] Therefore, testing for a significant PNH clone with flow cytometry, as done in the cases reviewed here, is important especially in non-responders to treatment for AA. This is highlighted in the case described here in which AA therapy was unsuccessful, and the patient was transfusion-dependent in the setting of ongoing hemolysis. In this case, eculizumab was initiated. Eculizumab binds to the complement component C5 and prevents its cleavage to C5a and C5b, which is required for formation of the membrane attack complex (MAC).[44] Red blood cells (RBCs) are normally protected from MAC formation by the GPI-linked protein CD59 on their surface; PNH RBCs lacking CD59 are susceptible to MAC formation. Eculizumab interferes with this step and thus reduces intravascular hemolysis. The efficacy of eculizumab was shown in two trials in PNH, the randomized controlled TRIUMPH study and the prospective SHEPHERD study.[45,46] Both studies demonstrated decreased transfusion requirements, improved laboratory indicators of ongoing hemolysis and better quality of life in the transfusion arm. These studies illustrate that the identification of a PNH clone is essential in the setting of AA, as well as when faced with pancytopenia in the setting of SLE, as eculizumab is an effective therapy. However, supportive care or steroids may be helpful as an initial therapy of PNH in the setting of SLE, as shown by the 3 previous cases reported here.

4.1.3 Conclusion

The diagnosis and treatment of AIMF, AA and PNH is challenging. Furthermore, when these are the first manifestation of SLE, the diagnosis of SLE and the attribution of bone marrow failure to SLE are even more challenging. Classification criteria for SLE such as the SLICC criteria, although primarily used for research purposes, are sometimes used when faced with difficulty in making an SLE diagnosis; however, they may be misleading when attempting to diagnose SLE in the setting of bone marrow failure. It is important to exclude primary myelofibrosis, AA or PNH in patients with pancytopenia since these patients may meet SLICC criteria for SLE, such as in cases 2.1.3 and 2.1.4 described here, even though SLE may not be the underlying cause. A correct differentiation of primary bone marrow failure from that attributable to SLE has important therapeutic implications. The elucidation of pathophysiological mechanisms behind bone marrow failure in SLE may allow for clinically useful biomarkers, and these cases illustrate that further research is warranted in this regard.

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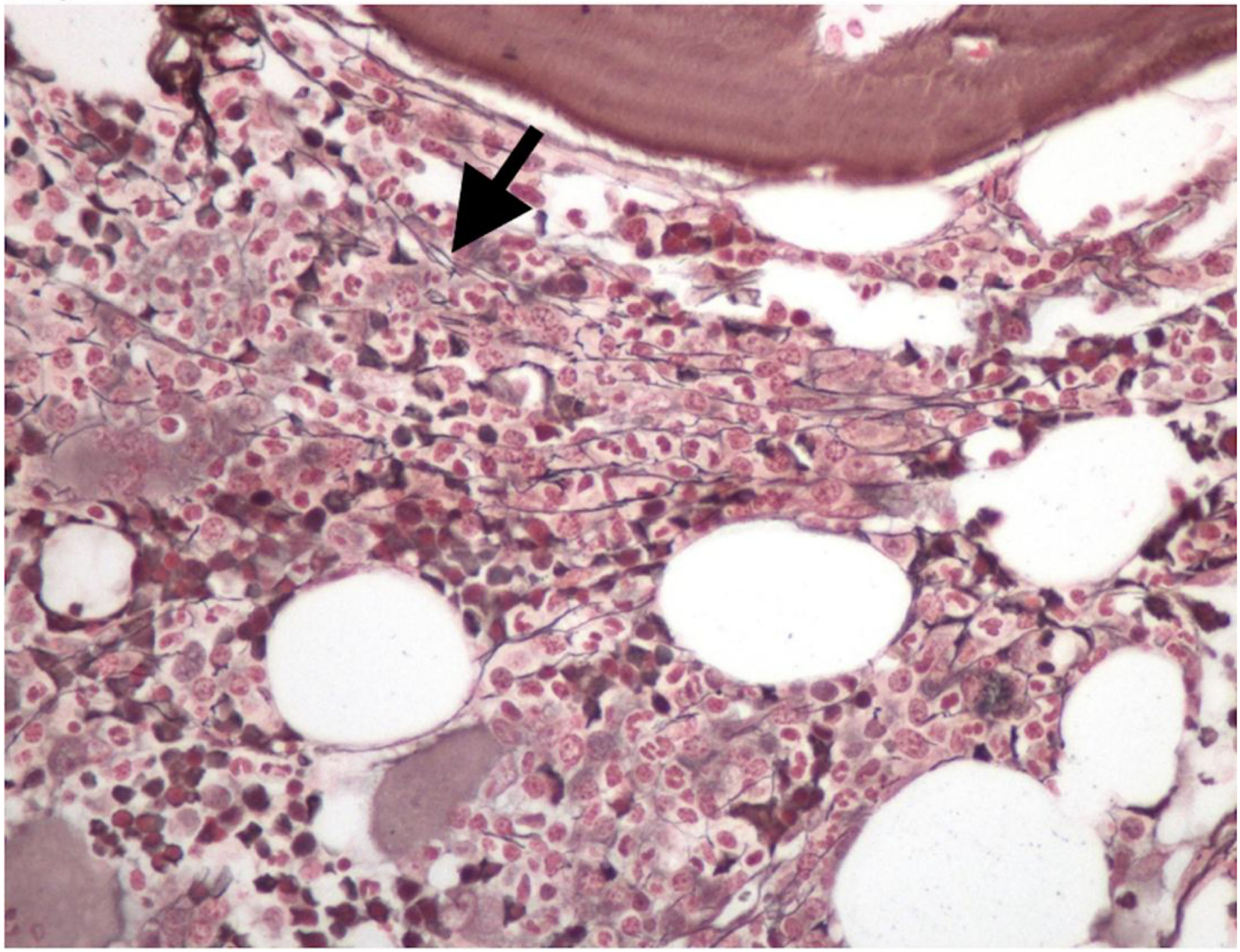

Figure 1.
mild to moderate increase in reticulin fibers (arrow), with grade 1 to 2 myelofibrosis, and no increase in collagen fibers

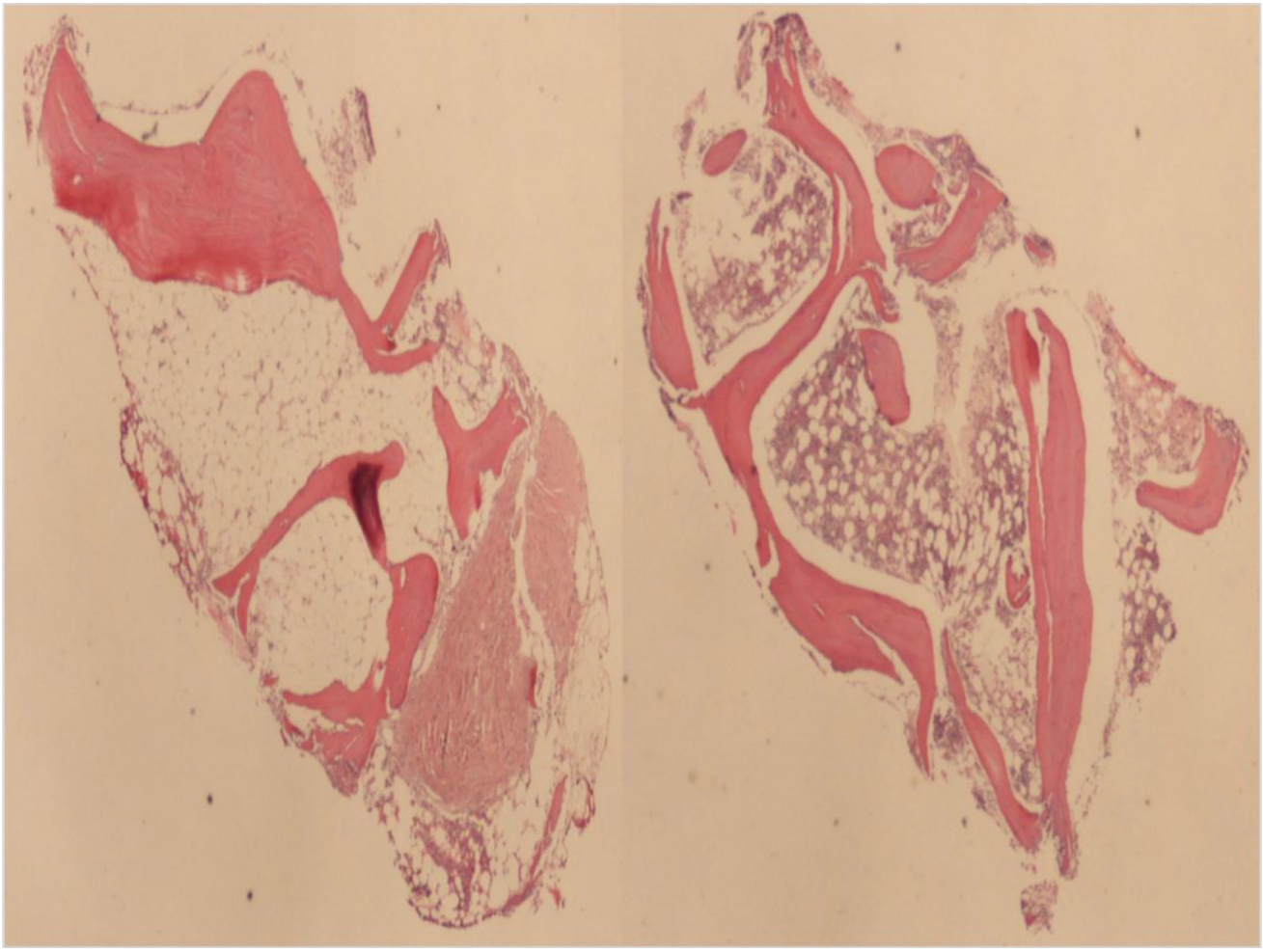

Figure 2.
hypocellularity in patient's biopsy sample (left image); normocellular marrow sample for comparison (right)

Table 1

Autoimmune Myelofibrosis: Demographic, Hematologic, and Immunologic Data

Reference	Age	Gender	WBC	Hb	Plt	Lymph	Neut	Retic Index	Smear Description	LDH	Haptoglobin	DAT	ANA	dsDNA	Splenomegaly	Other serology
Agarwal et al 1995	12	F	4.7	NR	4	3.3	0.7	NR	NR	NR	NR	−	1:40	−	−	NR
Aharon et al 1997; Amital et al 2003	54	F	3.1	5.1	96	0.6	2.2	NR	Burr, tear drop, anisocytosis, microcytosis, hypochromatosis, few ovalocytes & spherocytes	NR	NR	NR	high titer	+	+	hypocomplement, anticardiolipin, antihistone, anti-Ro
Aziz et al 2004	22	F	1.2	6.2	18	NR	NR	NR	Leukoerythroblasts, tear drop, nucleated red blood cells	NR	NR	NR	1:160	NR	+	hypocomplement
Borba et al 1993	39	F	2.4	9.7	341	−	0.36	0.2	NR	NR	NR	+	1:200	−	NR	hypocomplement, antineutrophil
Cavalcant et al 1978	29	M	4.1	4.3	186	0.94	3.1	0	NR	normal	normal	+	1:160	+	−	hypocomplement, + lupuserythematosus cell test
Chalayer et al 2014	17	F	0.48	2.9	15	0.08	0.28	0.2	No tear drops or leukoerythroblasts	NR	NR	−	1:1280	+	+	hypocomplement, anti-Ro, RNP 70, U1-RNP
Daly and Scott 1983	16	F	1.2	8	50	NR	0.6	6.6	Tear drop poikilocytes, rouleaux	NR	NR	−	1:1280	+	+	hypocomplement
Durupt et al 2000	29	F	1.1	9.4	102	0.3	0.6	NR	NR	NR	normal	−	1:1120	+	−	hypocomplement
el Mouzan et al 1988	13	F	1.3	6.5	10	1	0.2	0.1	Tear drops, mild hypochromia	NR	NR	+	1:640	+	+	hypocomplement, rheumatoid factor
Foley-Nolan et al 1992	20	F	4.5	10.5	45	1.9	1.3	NR	NR	NR	normal	+	1:800	+	−	hypocomplement, lymphocytotoxic antibody
Hirose et al 1993	54	F	1.7	6.9	17	NR	NR	NR	NR	NR	NR	NR	1:320	−	NR	hypocomplement, anticardiolipin, lupus anticoagulant
Inoue et al 1992	24	F	3.8	6.8	2	−	1	NR	NR	NR	NR	−	1:100	−	−	hypocomplement, antiplatelet
Kaelin & Spivak 1986	27	F	4.4	13.1	5	0.9	2.8	NR	NR	NR	normal	+	1:1280	+	−	hypocomplement, antiplatelet, antineutrophil, anti-Ro, anti-La
Kiss et al 2000	18	F	0.9	4.2	28	NR	NR	NR	NR	NR	NR	NR	high titer	−	−	hypocomplement, anticardiolipin
Lau et al 1969	25	F	2.7	8.3	26	NR	NR	1.3	Leukoerythroblastosis, myelocytes, erythroblasts, poikilocytes, elliptocytes	NR	NR	−	NR	NR	+	+ lupuserythematosus cell test
Matsuoka et al 1989	60	F	4	7	20	1.4	1.4	0.5	NR	NR	NR	−	1:320	+	Previous splenecto my	NR
Nanji & Jetha 1984	28	M	0.3	NR	1	NR	NR	NR	NR	normal	NR	−	1:40	+	+	NR
Paquette et al. 1994	68	M	3.5	5.7	222	NR	NR	0	NR	NR	NR	NR	1:5280	−	−	hypocomplement
Paquette et al 1994	27	F	5.9	5	1	NR	NR	0.7	Leukoerythroblastosis	NR	NR	+	1:80	−	+	hypocomplement
Paquette et al 1994	23	F	4.2	9.5	55	NR	NR	NR	NR	NR	NR	NR	high titer	NR	+	hypocomplement
Paquette et al 1994	56	F	5.4	9.7	76	NR	NR	1.4	Myelocytes, metamyelocytes, nucleated red blood cells, tear drop	NR	NR	−	high titer	+	−	hypocomplement
Paquette et al 1994	18	F	7.7	2.7	4	NR	NR	0.5	Leukoerythroblastosis	NR	NR	+	high titer	+	+	hypocomplement
Paquette et al 1994	70	F	3.8	4.2	20	NR	NR	NR	Leukoerythroblastosis	NR	NR	+	high titer	−	−	hypocomplement

Reference	Age	Gender	WBC	Hb	Plt	Lymph	Neut	Retic Index	Smear Description	LDH	Haptoglobin	DAT	ANA	dsDNA	Splenomegaly	Other serology
Paquette et al 1994	62	F	3	9.3	35	NR	NR	NR	NR	NR	NR	NR	high titer	−	+	hypocomplement
Paquette et al 1994	69	F	6.8	6.8	39	NR	NR	NR	NR	NR	NR	NR	high titer	−	+	hypocomplement
Pillai et al 2009	40	F	1.2	10.6	25	NR	0	Normal reticcount	NR	normal	high	+	1:320	−	−	hypocomplement
Ramakrishna et al 1995	18	F	6	5.4	30	NR	NR	NR	Anisocytosis, polychromasia, poikilocytes, spherocytes, microcytes, leukoerythroblasts	NR	low	+	1:2560	+	−	hypocomplement, lupus anticoagulant anticardiolipin, antiplatelet
Sacre et al 2010	44	F	NR	7	65	NR	NR	2.5	Tear drops, leukoerythroblasts	NR	normal	−	high titer	+	−	NR
Sarkar et al 2009	45	M	2.5	5.3	25	1	1.2	NR	NR	high	normal	+	1:640	+	−	NR
Ungprasert et al 2016	33	F	1.8	6.8	60	0.48	NR	NR	No evidence of hemolysis	NR	NR	−	1:640	+	NR	hypocomplement
Vora et al 1998	22	F	4.7	6.4	7	NR	NR	NR	NR	NR	NR	NR	1:1000	−	+	NR
Case 2.1.1	69	F	2.3	8.6	19	0.4	1.9	0.3	Poikilocytes	high	low	−	1:1280	+	−	hypocomplement
Case 2.1.2	55	F	2.2	7.3	23	0.9	2	0.6	Slight schistocytes, tear drops, poikilocytes	high	low	+	1:2560	+	−	hypocomplement

Key: WBC: white blood cell count (× 10^9/L); Hb: hemoglobin (g/dL); Plt: platelet count (× 10^9/L); Lymph: lymphocyte count (× 10^9/L); Neut: neutrophil count (× 10^9/L); Retic index: reticulocyte index; LDH: lactate dehydrogenase; DAT: direct antiglobulin test (Coombs'); ANA: antinuclear antibody titer; dsDNA: double-stranded DNA titer; NR: not reported; "−": negative; "+": positive

Table 2

Aplastic Anemia: Demographic, Hematologic, and Immunologic Data

Reference	Age	Sex	WBC	Hb	Plt	Lymph	Neut	Retic Index	Smear	LDH	Haptoglobin	DAT	ANA	dsDNA	Splenomegaly	PNH test	Serum inhibitor found?	Other serology
Abdou et al 1981	24	F	2.8	8	98	NR	NR	NR	NR	NR	NR	NR	1:2560	+	NR	NR	Y (complement dependent anti-DNA IgG antibody)	hypocomplement
Ahmad et al 2011	26	F	2.5	7.5	91	NR	1.2	0	Hypochromic red cells	NR	NR	−	high	+	+	NR	N	NR
Alishiri et al 2012	29	F	1.3	5.2	12	NR	NR	NR	NR	NR	NR	−	high	+	NR	NR	N	NR
Bailey et al 1989	17	F	0.3	NR	37	0.1	0.2	NR	NR	NR	NR	−	1:640	+	NR	NR	Y (non-complement dependent antineutrophil IgG antibody)	hypocomplement
Baumann et al 2011	54	F	0.8	2.3	295	NR	0.1	0.1	NR	high	low	+	1:30,720	+	previous splenomegaly	flow cytometry negative	N	hypocomplement, anti-cardiolipin IgM, antibeta-2 glycoprotein IgM
Brooks Jr. et al 1984	17	F	0.5	9.7	121	0.4	0	0.4	NR	NR	NR	+	high	+	NR	NR	Y (complement dependent IgG antibody)	hypocomplement, anti-Ro
Chalayer et al 2015	23	F	2.62	8	19	0.63	1.8	NR	NR	NR	NR	−	1:2,560	−	NR	NR	NR	antiplatelet, anti-Ro, anti-La
Chute et al 1996	33	M	2.8	11.5	96	NR	NR	NR	NR	NR	NR	NR	high	+	NR	NR	N	anti-Smith
Chute et al 1996	35	F	0.4	8.6	99	NR	NR	NR	NR	NR	NR	−	1:320	−	NR	NR	N	anti-Smith, antiphosph olipid
Fitchen et al 1979	36	F	3.4	3.5	20	1.4	1.7	0	NR	NR	NR	+	1:160	NR	−	NR	Y (complement dependent IgG antibody)	NR
Hinterberger-Fischer et al 1989	74	F	3	TD	82	NR	NR	NR	NR	NR	NR	NR	high	NR	NR	NR	NR	NR
Liu et al 2014	25	F	0.9	3.8	3	NR	NR	NR	NR	NR	NR	−	high	−	−	NR	NR	anti-nRNP, antihistone
Marques et al 1995	41	F	2.6	7.9	4	NR	NR	NR	NR	NR	NR	NR	1:40	−	NR	NR	Y (unidentified)	hypocomplement
Morishita et al 1997	26	F	NR	TD	3	1.6	NR	NR	NR	NR	NR	N	1:1280	+	NR	NR	NR	hypocomplement, antiplatelet, + lupus erythematosus cell test
Pavithran et al 2003	32	F	2.3	6.5	45	2	0.3	0.1	NR	NR	NR	NR	high	+	NR	NR	NR	+ lupus erythematosus cell test
Roffe et al 1991	31	F	1.9	8.1	17	NR	NR	NR	NR	NR	NR	−	1:640	+	NR	Ham -	Y (unidentified)	hypocomplement
Seo et al 2011	52	F	2.5	4.5	55	0.2	1.4	0.3	Increased myelocytes, no definitive abnormal cells	NR	NR	NR	1:320	+	+	NR	NR	hypocomplement, anti-Ro

Reference	Age	Sex	WBC	Hb	Plt	Lymph	Neut	Retic Index	Smear	LDH	Haptoglobin	DAT	ANA	dsDNA	Splenomegaly	PNH test	Serum inhibitor found?	Other serology
Singh et al 2004	22	F	1.3	4.8	23	0.4	0.8	0	Suggestive of dimorphic anemia	NR	NR	NR	high	NR	+	NR	NR	NR
Stricker et al 1984	28	F	1.5	TD	51	NR	0.5	0.1	NR	NR	NR	−	high	+	NR	NR	NR	hypocomplement, + lupus erythematosus cell test
Stricker et al 1984	30	F	0.5	NR	14	NR	0.22	NR	NR	NR	NR	−	1:2560	+	NR	NR	NR	NR
Sumimoto et al 1991	6	F	0.6	4.8	5	0.6	0	NR	NR	NR	NR	−	high	+	NR	NR	N	+ lupus erythematosus cell test
Tabushi et al 2003	56	F	2.5	6	40	1.8	0.6	0.2	NR	high	normal	−	1:40	+	NR	NR	NR	hypocomplement, lupus anticoagulant
Tagoe et al 2001	26	M	4.7	4.4	79	0.4	3.6	NR	NR	NR	NR	+	1:80	+	−	Ham -	NR	hypocomplement
Tagoe et al 2001	24	F	0.4	8	15	0.4	0	NR	NR	NR	NR	NR	high	+	−	NR	NR	hypocomplement, lupus anticoagulant
Walport et al 1982	25	F	0.5	7	45	NR	0	0.3	NR	NR	NR	−	high	+	NR	NR	NR	hypocomplement
Winkler et al 1988	48	F	1.7	10.4	100	0.54	0.9	0.3	NR	NR	NR	+	1:10,240	+	+	NR	NR	hypocomplement, antiplatelet
Case 2.1.3	67	F	3.3	6.3	4	1.9	0.82	0.2	Poikilocytosis	low	high	NR	1:1280	+	−	NR	NR	hypocomplement, antiplatelet, anti-Ro, anti-LA

Key: WBC: white blood cell count (× 10^9/L); Hb: hemoglobin (g/dL); Plt: platelet count (× 10^9/L); Lymph: lymphocyte count (× 10^9/L); Neut: neutrophil count (× 10^9/L); Retic index: reticulocyte index; LDH: lactate dehydrogenase; DAT: direct antiglobulin test (Coombs'); ANA: antinuclear antibody titer; dsDNA: double-stranded DNA titer; NR: not reported; "−": negative; "+": positive

Table 3

Paroxysmal Nocturnal Hemoglobinuria: Demographic, Hematologic and Immunologic Data

Reference	Age	Gender	WBC	Hb	Plt	Lymph	Neut	Retic Index	Smear	LDH	Hapto-globin	DAT	ANA	dsDNA	Splen-omegaly	PNH diagnosis	Serum inhibitor found?	Other serology
Gupta et al 2009	60	F	2.9	11	11	NR	NR	NR	NR	high	low	−	1:1280	+	NR	Flow cytometry: CD55 & 59 deficiency; Ham +; sugar water +	NR	hypocomplement
Kontomanolis et al 2013	27	F	NR	N	3	NR	NR	NR	NR	NR	NR	NR	+	+	NR	Flow cytometry: CD55 & 59 deficiency	NR	anti-Ro
Nakamura et al 2011	29	F	11.4	7.3	42	NR	NR	NR	NR	high	low	−	+	−	NR	Flow cytometry: CD55 & 59 deficiency; Ham +; sugar water +	NR	NR
Case 2.1.4	70	F	2.4	8.9	2	0.8	0.66	0.5	Poikilocytosis, macrocytosis	high	low	+	1:1280	+	−	Flow cytometry: > 20% PNH clone	NR	lupus anticoagulant
9	6	h	80															

Key: WBC: white blood cell count (× 10^9/L); Hb: hemoglobin (g/dL); Plt: platelet count (× 10^9/L); Lymph: lymphocyte count (× 10^9/L); Neut: neutrophil count (× 10^9/L); Retic index: reticulocyte index; LDH: lactate dehydrogenase; DAT: direct antiglobulin test (Coombs'); ANA: antinuclear antibody titer; dsDNA: double-stranded DNA titer; NR: not reported; "−": negative; "+": positive

Table 4

Autoimmune Myelofibrosis: Bone Marrow Findings, Treatment and Response

Reference	Age	Gender	Bone Marrow Finding	Treatment	Response
Agarwal et al 1995	12	F	Hypocellular marrow with residual patches of hematopoetic cells with diffuse grade III fibrosis	Prednisolone 2 mg/kg/day	Improvement
Aharon et al 1997	54	F	Focal hypercellularity, many reticulin and collagen fibers, mild megakaryocytosis, normal appearance of the red and white cell lines	Prednisone 80 mg daily for 3 weeks: no improvement; IVIG 400 mg/kg/day for 5 days	Improvement
Aziz et al 2004	22	M	Increased cellularity with increased number of megakaryocytes without increase in blasts; silver stain showed increased reticulin fibrosis and patchy areas of collagenized marrow	Prednisone 1 mg/kg, tapered over several weeks	Improvement
Chalayer et al 2014	17	F	Hypercellular marrow with focal lymphocytic infiltration, dysmyelopoesis, erythrophagocytosis, grade I-II fibrosis	Methylprednisolone 500 mg/day for 3 days, hydroxychloroquine, prednisone 1 mg/kg: no improvement; IVIG 30 g/day for 4 days	Improvement
Borba et al 1993	39	F	Normal hematopoetic elements with fibrosis areas; reticulin moderately increased on Gomori stain	Pulse methylprednisolone with prednisone 10 mg/day: not significant improvement; Plasma exchange for 6 sessions, repeat methylprednisolone pulse, prednisone 20 mg/day, cyclophosphamide 100 mg/day	Improvement
Cavalcant et al 1978	29	M	Marked hypercellularity and paucity of erythroid differentiation; Gomori stain showed extensive and diffuse increase in reticulin	Prednisone 60 mg/day tapered over 92 days	Improvement
Daly et al 1983	16	F	Marked marrow fibrosis with reduced numbers of erythroid precursors; megakaryocytes were plentiful; reticulin content was greatly increased	Prednisolone 30 mg/day	Improvement
Durupt et al 2000	29	F	All normal hematopoietic elements with a small increase of mature megakaryocytes and marked inflammatory medullar reaction with plasmocytosis; systemized increase in reticulin	Glucocorticoids 2 mg/kg, cyclosporine 5 mg/kg	Improvement
El Mouzan et al 1988	13	F	Decrease in bone marrow hematopoietic activity with myeloid to erythroid ratio 1:1, normal megakaryocytes, increased reticuloendothelial activity and fibrosis	Prednisolone 30 mg/day	Improvement
Foley-Nolan et al 1992	20	F	Hypercellular with marked increase in number of megakaryocytes; reticulin content increased diffusely and significantly	Prednisolone 40 mg/day, azathioprine 50 mg/day then increased to prednisolone 60 mg/day, azathioprine 150 mg/day	Improvement
Hirose et al 1993	54	F	Marked marrow fibrosis with reduced numbers of erythroid precursors and normal proliferation of both megakaryocytes and myeloid series; reticulin content increased with no evidence of malignancy	Methylprednisolone 1 g/day for 3 days then prednisolone 60 mg/day	Improvement
Inoue et al 1992	24	F	Marked hyperplastic marrow with increase in reticulin fibers; all elements including megakaryocytes increased in number	Prednisolone 1.2 mg/kg, then pulse therapy methylprednisolone 1 g/day for 3 days	Improvement
Kaelin et al 1986	27	F	Normal hematopoietic elements with slight increase in mature megakaryocytes; reticulin markedly increased	Methylprednisolone 100 mg every 6 hours	Improvement
Kiss et al 2000	18	F	Significant increase (40%) in the amount of reticulin fibres (Beumaister 3–4), hypocellularity of the myeloid components and a massive lymphocytic infiltration (mainly of B cells with some CD8 positive T cells).	Methylprednisolone 1 g/day for 3 days then 2 mg/kg/day steroid + 3 mg/kg cyclosporine + 5×3 million IU Neupogen: poor response Azathioprine 50 mg daily: improvement, then relapse Steroid 1 mg/kg daily: improvement	Improvement

Reference	Age	Gender	Bone Marrow Finding	Treatment	Response
Lau et al 1969	25	F	Active myelosclerosis with increased osteosclerosis and moderately increased reticulin together with a well-marked necrotic element	Steroid	Improvement
Matsouka et al 1989	60	F	Presence of dense fibrous tissue with fibroblast; paucity of immature and polymorphonuclear cells	Hydrocortisone 1 g/day	Deceased
Nanji et al 1984	28	M	Variable cellularity - hypocellular in some areas and hypercellular in others; megakaryocytes decreased in number; myeloid and erythroid activity present; extensive fibrosis and diffuse increase in reticulin	Corticosteroids prior to diagnosis of SLE	Deceased
Paquette et al 1994	68	M	Hypercellular marrow with increased stroma and reticulin fibrosis	Prednisone 20 mg/day	Improvement
			Repeat biopsy 3 months later: hypercellularity with fibrosis and lymphoid aggregate composed of mature lymphocytes		
Paquette et al 1994	27	F	Marked fibrosis with clustering of megakaryocytes	Prednisone 60 mg daily	Improvement
Paquette et al 1994	23	F	Fibrosis and open sinusoids with megakaryocyte clusters	Prednisone 50 mg daily	Improvement
Paquette et al 1994	56	F	Fibroblast proliferation and reticulin fibrosis prominent; erythroid hyperplasia and increased megakaryocytes	Prednisone	No improvement
Paquette et al 1994	18	F	Early myelofibrosis with a hypercellular marrow; increased megakaryocytes with clustering	Prednisone 80 mg daily	Improvement
Paquette et al 1994	70	F	Advanced myelofibrosis with a hypocellular marrow; predominance of megakaryocytes	High dose prednisone	Deceased
Paquette et al 1994	58	F	Advanced myelofibrosis with a hypocellular marrow; marked osteosclerosis	NR	Deceased
Paquette et al 1994	69	F	Stroma moderately increased with accumulation of fibrillar reticulin; hypercellularity with increased megakaryocytes with clustering	Prednisone	Improvement
Pillai et al 2009	40	F	Hypercellular with increased megakaryocytes and reticulin	Methylprednisolone 500 mg daily for 5 days and prednisolone 60 mg daily	Improvement
Ramakrishna et al 1995	18	F	Markedly hypercellular marrow with erythroid hyperplasia, plentiful megakaryocytes and markedly increased reticulin	Prednisolone 75 mg/day then prednisolone 50 mg/day with vincristine, colchicine, and IVIG	Improvement
Sacre et al 2010	44	F	Hypercellularity with marked reticulin fibrosis without myelodysplasia	Prednisone 1 mg/kg/d with IVIG	Improvement
Sarkar et al 2009	45	M	Hypercellular marrow with focal lymphocytic infiltration and moderate fibrosis	Prednisone 60 mg daily	Improvement
Ungprasert et al 2016	33	F	Normocellular marrow with myelofibrosis grade III and increased atypical megakaryocytes	Prednisone 60 mg daily	Improvement
Vora et al 1998	22	F	Marked osteomyelosclerosis with severe myelofibrosis of the marrow spaces and total effacement of normal haematopoiesis together with irregular thickened trabeculae showing osteosclerosis	Plasma exchange: no benefit; pulse methylprednisolone 1 g/day for 3 days	Improvement
Case 2.1.1	69	F	Reticulin fibrosis with plasmacytosis	High dose steroids: poor response; IVIG 1g/kg/day for 5 days, azathioprine 50 mg twice daily	Improvement
Case 2.1.2	55	F	Reticulin fibrosis with plasmacytosis	High dose steroids, IVIG	Deceased

Table 5

Aplastic Anemia: Bone Marrow Findings, Treatment and Response

Reference	Age	Gender	Bone Marrow Finding Reported	Treatment	Response
Abdou et al 1981	20	F	Hypocellularity of all cell lines and a left shift of myeloid	Plasmapheresis for 12 days	Improvement
Ahmad et al 2011	26	F	series Hypocellular with depressed hematopoiesis and normal reticulin pattern	Oral steroids	Improvement
Alishiri et al 2012	29	F	Hypocellular with less than 10% cellularity	Pulse methylprednisolone 1g/day for 3 days cyclophosphamide 250 mg/day for 2 months: poor response cyclosporine 300mg/day × 2 months: poor response rituximab	Improvement
Bailey et al 1989	17	F	Severe hypoplasia with cellularity 5% with no maturing myeloid elements, megakaryocytes, or megaloblastic erythroid changes	Methylprednisolone 40 mg/day: poor response plasmapheresis for 6 sessions with methylprednisolone	Improvement
Baumann et al 2011	54	F	Hypocellularity	Prednisolone 100 mg/day	Improvement
Brooks Jr. et al 1984	17	F	Severe aplastic anemia	Plasmapheresis for 4 sessions	Improvement
Chalayer et al 2014	22	F	Hypocellular marrow with < 10% cellularity and plentiful megakaryocytes	Prednisone 1 mg/kg for 1 month: poor response cyclosporine + rabbit antithymocyte globulin: poor response cyclosporine + horse antithymocyte globulin: poor response IVIG	Improvement
Chute et al 1996	33	M	Hypocellularity without fibrosis	Hydroxychloroquine 200 mg twice daily	Improvement
Chute et al 1996	35	F	Hypocellularity (80% fat, 20% cell), and no evidence of leukemia. T-cell lymphocyte predominance: CD7 positive (early T cell antigen)	Prednisone 1 mg/kg/day	Improvement
Fitchen et al 1979	36	F	Hypocellular marrow without malignant cells	Androgen therapy, high dose methylprednisolone: poor response; plasma exchange for 4 sessions, then monthly	Improvement
Hinterberger-Fischer et al 1989	74	F	NR	Cyclosporin A	Improvement
Liu et al 2014	25	F	Hypocellular with < 20% cellularity, absent megakaryocytes and fatty change	Methylprednisolone 500 mg/day for 4 days + IVIG then prednisolone 10mg/day +cyclosporine: poor response rituximab: poor response rabbit antithymocyte globulin then cyclosporine 300 mg/day and G-CSF	Improvement
Marques et al 1995	41	F	Very hypocellular bone marrow with adequate stainable iron	Methylprednisolone 500 mg×2 days, then IVIG for 5 days: poor response Plasmapheresis + cyclophosphamide	Improvement
Meyerson et al 1994	41	F	Severe marrow hypoplasia involving all cell lines with 1015% cellularity	Antithymocyte globulin + cyclosporine + methylprednisolone	Deceased

Reference	Age	Gender	Bone Marrow Finding Reported	Treatment	Response
Morishita et al 1997	26	F	Marked decrease in megakaryocyte production with severe hypoplasia of the trilineage cells	Pulse methylprednisolone 1 g/day for 3 days: poor response Antithymocyte globulin + cyclosporin A with G-CSF	Deceased
Pavithran et al 2002	32	F	Aplastic marrow with few areas of hematopoietic elements	Prednisolone 80 mg/day followed by methylprednisolone 1 g/day for 4 days: poor response	Deceased
Roffe et al 1991	31	F	Aplastic anemia	Methylprednisolone 1g IV followed by cyclophosphamide 2 mg/kg IV	Improvement
Seo et al 2011	52	F	Hypocellular marrow with cellularity 10–30% and many fatty globules without neoplastic infiltration or significant myelofibrosis	Prednisolone 1mg/kg/day + cyclosporine 100 mg/day + hydroxychloroquine	Improvement
Singh et al 2004	22	F	Hypocellular marrow with fatty infiltration and decreased precursors of all three lineages	Pulse methylprednisolone for 3 days: poor response pulse cyclophosphamide + prednisolone: poor response cyclosporine 150 mg BID	Improvement
Stricker et al 1984	19	F	Severe hypoplasia (<10% cellularity) with focal nests of lymphocytes and plasma cells and markedly decreased megakaryocytes	Prednisone 100 mg daily + oxymethaolone	Improvement
Stricker et al 1984	25	F	Severe hypoplasia (<10% cellularity)	Oxymethaolone	Improvement
Sumimoto et al 1991	6	F	Hypocellular; predominance of premature cells with maturation arrest and low CD4:CD8 ratio	Pulse methylprednisolone	Improvement
Tabushi et al 2003	42	F	Hypocellularity without proliferation of blasts, dysplastic changes of trilineage and fibrosis	G-CSF + cyclosporine + antithymocyte globulin	Deceased
Tagoe et al 2001	19	F	Hypocellularity, decreased erythroid series, relatively increased plasma cells, mild immaturity, and no evidence of malignancy	Prednisone 60 mg daily + hydroxychloroquine 200 mg twice daily	Improved
Tagoe et al 2001	24	F	Aplasia with a striking decrease of all 3 cell lines, and marked increase in plasma cells with a small area of megakaryocytes	Methylprednisolone 48 mg daily	Improved
Walport et al 1982	22	F	Hypocellular fragments with cell trails showing reduction of all haemopoietic cell lines	Oral prednisolone + cyclophosphamide	Improved
Winkler et al 1988	48	F	Marrow hypoplasia with 10% cellularity	Plasmapheresis + cyclophosphamide: poor outcome; high dose IV cyclophosphamide	Improvement

Table 6

Paroxysmal Nocturnal Hemoglobinuria: Bone Marrow Findings, Treatment and Response

Reference	Age	Gender	Bone Marrow Finding Reported	Treatment	Response
Gupta et al 2009	60	F	Many megakaryocytes	Supportive care	Improved
Kontomanolis et al 2013	27	F	NR	Steroids	Improved
Nakamura et al 2011	29	F	NR	Steroids	Improved
Case 4	70	F	1st biopsy: polyclonal B lymphocytosis and plasmacytosis 2nd biopsy: patchy hypocellularity	Steroids, IVIG, rituximab antithymocyte globulin and cyclosporineeculizumab	Stable