Chapter 3
Anemia and Thrombocytopenia

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Outline

Anemia and thrombocytopenia are relevant findings in the clinical assessment of systemic sclerosis patients and several mechanism of actions are involved in the determination of these complications. Studies on the prevalence of anemia in SSc suggest that its prevalence is 25–40% [1], with higher prevalence in those with early diffuse disease [2] and in Caucasians [3]. Anemia has been included in the 5-item prediction rule for 2 and 5 year mortality in SSc patients with early diffuse disease. Even moderate anemia (Hb < 10 mg/

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dL) represents an independent risk factor for mortality (HR 1.88/4.57) [2, 4, 5].

In another aspect of SSc,the PHAROS registry study highlighted that, in SSc patients at risk to develop pulmonary arterial hypertension (PAH), anemia was strongly associated with higher mortality [6], while another prospective study suggested that anemia is the only laboratory risk factor associated with the development of PAH [7].

Anemia of chronic illness is commonly observed in systemic sclerosis, but several other disease-specific vascular complications can exacerbate it, as noted above, including scleroderma renal crisis. Other causes of anemia, less frequent and less well-defined in SSc, such as autoimmune and drug-induced anemia, will also be discussed.

The most common complications characterized by the association between anemia and thrombocytopenia, such as scleroderma renal crisis, thrombotic thrombocytopenic purpura and atypical haemolytic uremic syndrome will be analysed and compared, providing points for differential diagnosis and treatment.

In addition other conditions associated with the simultaneous presence of anemia and thrombocytopenia will be discussed.

Nutritional Deficit Anemia

Iron-deficiency has been documented in 16.4/18.35% patients with systemic sclerosis [8]. Gastric antral vascular ectasia (GAVE, watermelon stomach) is one of the most frequent causes of this nutritional-related type of anemia in SSc patients. It is mostly prevalent in early diffuse cutaneous systemic sclerosis with rapid skin progression and a distinct antibody profile (anti-RNA polymerase III positivity) [9].

GAVE is represented by chronic gastrointestinal bleeding and iron deficiency anemia and it corresponds to a characteristic endoscopic finding of longitudinal rows of sacculated and dilated mucosal vessels in the antrum of the stomach.

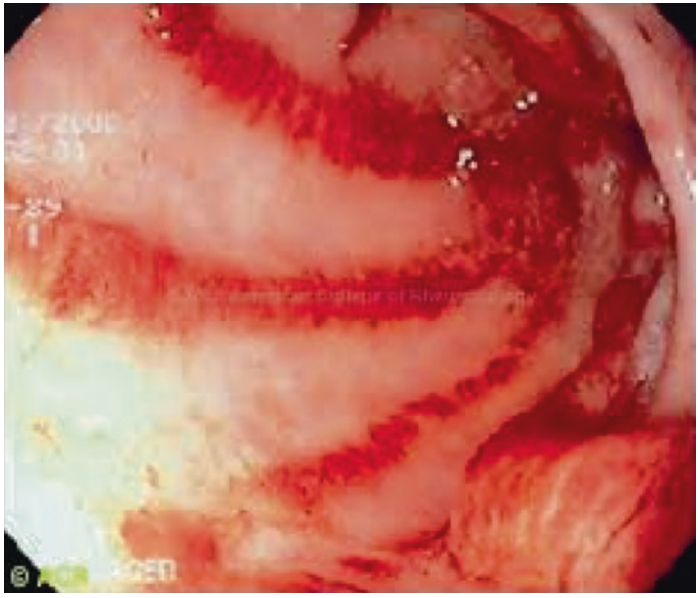

FIGURE 3.1 Watermelon stomach. An endoscopic view of a Gastric Antral Vascular Ectasia (GAVE). Note the longitudinal rows of vessels in the stomach resembling the stripes of a watermelon. "Courtesy of PathologyOutline.com"

This is said to resemble the stripes on a watermelon [10] (Fig. 3.1).

Several hypotheses have been proposed to explain the pathogenesis of GAVE. One possibility is the prolapse of the antral mucosa due to alterations in the connection between the distal gastric mucosa and the adjacent muscularis externa or in peristalsis. More recently it has been suggested that GAVE is a possible disease-specific vascular manifestation of systemic sclerosis, according to the evidence that up to 60% of GAVE patients have skin telangiectasias. A third theory supports a link between GAVE and autoimmunity suggesting a possible cross-reactivity with specific proteins in the gastric mucosa and submucosa.

Most of the patients present either with symptomatic iron deficiency anemia (weakness, fatigue, or dyspnea) or asymptomatic anemia (with laboratory findings like low hemoglobin and mean corpuscular volume). Patients affected by diffuse systemic sclerosis can present with occult fecal blood, hematochezia, or hematemesis. Indeed, it has been reported that GAVE can occur also in the lower GI tract or even in the rectum [11], so clinical presentation should direct the appropriate GI tract to study first.

Digestive endoscopy is the gold standard for the diagnosis of GAVE and enteroscopy, red blood cell scan, and video capsule endoscopy are useful aids and provide significant help to differentiate it from AV malformations, venous ectasia, gastric telangiectasia, hemangioma, and angiosarcoma.

Most importantly, the rheumatologist should suspect GAVE in a clinical setting when the anemia is refractory. Given that the mean of time between the beginning of the disease and the diagnosis of GAVE is 3 years, with a mean hemoglobin of 8.2 g/dL, a high index of suspicion, especially in patients with early disease, is important.

Because more than 90% of SSc patients have gastrointestinal disturbances, such as malabsorption and small intestinal bacterial overgrowth (SIBO), other nutritional deficits (vitamin B12, folic acid) should be considered as possible causes of nutrient-related anemia.

Recent data confirm that up to 70% of SSc patients might be considered as vitamin B12-deficient and half of them show a severe deficiency (<200 pg/mL) [12]. Notably a case report strongly linked the subcutaneous administration of vitamin B12 with sclerodermoid reaction at the site of injection [13], compatible with the histology of localized scleroderma. Few case reports detail of the occurrence of pernicious anemia in systemic sclerosis [14].

Of note, multifactorial causes of anemia should be always considered since data confirm that different causes of anemia can coexist in the same patient, such as GAVE and pernicious anemia [15] or more complex case reports of overlap syndromes with pernicious anemia [16]. The presence of a nor-

mochromic, normocytic anemia should not stop further lab tests to exclude nutritional deficits or the presence of overlapping causes. Treatment of GAVE can be very challenging and iron supplementation is often not effective; case reports suggest that the combination of methylprednisone and cyclophosphamide, or cyclophosphamide alone, can result in improvement [17, 18]. Autologous stem cell transplantation [19] has also been effective, despite some case reports described the occurrence of GAVE after hematopoietic stem cell transplant (HSCT-GAVE) [20].

Autoimmune Causes of Isolated Anemia and Thrombocytopenia

Compared to the other causes of anemia and thrombocytopenia, evidence for an autoimmune-mediated process are surprisingly scarce in SSc, while frequently reported in overlap syndromes [21] and supported by case reports [22–25]. The diagnosis of autoimmune anemia is based on the presence of signs of haemolysis with reticulocytosis, low haptoglobin, increased lactate dehydrogenase, elevated indirect bilirubin, and a positive direct antiglobulin test (Coombs test).

A case of a SSc patient associated with deficiency of IgA and the C4 component of complement associated with haemolytic anemia further compounds the complexity of the approach necessary to unearth the potential causes of anemia in SSc [26].

The diagnosis of immune thrombocytopenic purpura relies on the exclusion of several known triggers, such as viral infection, lymphoproliferative disorders and genetic diseases. Although it is possible in some settings to identify antiplatelet antibodies, the diagnosis remains clinical. Some cases confirm this association, for example evidence of the presence of anti-platelet antibodies against gpIIb/IIIa in systemic sclerosis [27] and the overlap between autoimmune hepatitis, immune thrombocytopenia and systemic sclerosis [28]. In addition, the occurrence of autoantibody against

thrombopoietin receptor has been demonstrated in the serum of a SSc patient with evidence of amegakaryocytic thrombocytopenia [29].

Microangiopathic Anemia and Thrombocytopenia

A microangiopathic heamolytic anemia associated with thrombocytopenia can be one of the peculiar aspects of the scleroderma renal crisis (SRC). SRC can be a life-threatening complication with heterogeneous presentations ranging from a sudden onset of accelerated arterial hypertension and rapidly progressive oliguric renal failure, to less intense elevations in blood pressure and less drastic renal alteration. Rare normotensive SRC has also been documented [30].

In the kidney of a SSc patient with scleroderma renal crisis, the vascular endothelial injury results in obliteration of the renal arcuate and interlobular arteries with consequent reduction in renal blood flow along with hyperplasia of renal juxtaglomerular cells. This sequence of events starts an inappropriate activation of renin and angiotensin leading, therefore, to renal vasoconstriction that eventually causes (frequently malignant) hypertension.

A microangiopathic hemolytic anemia (MAHA) results from fragmentation of red blood cells as they pass through renal vessels occluded by fibrin or platelet thrombi, while thrombocytopenia is the direct consequence of continuous platelet activation and consumption at damaged endothelial sites.

Other thrombotic microangiopathies can present with widespread microvascular thrombosis, thrombocytopenia, and microangiopathic hemolytic anemia (MAHA). These microangiopathies include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS).

HUS is traditionally distinguished as typical (Shiga and Shiga like toxin-associated) and atypical (alternative activation of complement pathway).

Histologically, on renal biopsy, aHUS is indistinguishable from HUS caused by toxin-producing bacteria or TTP.

Indeed, the differential diagnosis between scleroderma renal crisis, thrombotic thrombocytopenic purpura and haemolytic uremic syndrome is probably the most challenging differential in the approach of a SSc patient presenting with thrombocytopenia and haemolytic anemia [31]. Compared to SRC, TTP shows several common clinical presenting features, such as thrombocytopenia, MAHA, elevation of bilirubin and LDH, negative Coombs test and the presence of schistocytes, neurologic dysfunction, thrombotic microangiopathy and acute renal impairment and normal PT and PTT [32, 33].

Relevant differences on the other hand are as follows: hypertension is almost always present in SRC while is possible in TTP, SRC is commonly observed in the diffuse form of SSc while TTP occurs more frequently in the limited form of SSc and most importantly SRC responds to ACEi while TTP requires plasmapheresis.

This difference is mainly based on the pathophysiologic evidence that TTP is due to a reduced or absent activity of the von Willenbrand factor-cleaving protease activity, belonging to the group of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), which can be successfully treated by plasma exchange, in association with antiplatelet agents and anticoagulants, according to platelet count, and steroids. SRC is mainly dependent on aberrant activation of the renin-angiotensin system and thus appropriate therapy directed against this system is the most indicated approach and reduced consistently the rate of mortality for this complication.

Indeed, the exclusion of aHUS remains a critical issue for the multiple similarities with TTP and SRC; the levels of C3 are reduced only in less than half of the cases. It is generally accepted that if ADAMTS13 levels are >5% and the patient is resistant to plasma exchange, then the diagnosis is more likely to be aHUS than TTP. Despite the challenge of diagnosing aHUS, a new monoclonal antibody was recently approved for the treatment of aHUS [34].

Eculizumab is a recombinant, fully humanized monoclonal antibody, with a high binding affinity for C5 thus preventing

the formation of C5a and C5a-9 and it has been successfully employed also in patients with SSc [35]. Whether the efficacy of this therapy is due to the activation of complement in misdiagnosed SRC, still remains unclear and this clue offers future direction for research [36].

Drug-Induced Anemia and Thrombocytopenia

Several medications have been associated with the occurrence of anemia and thrombocytopenia in SSc. These include mainly drugs employed for specific SSc-related indications. In SSc patients treated with bosentan for digital ulcers, anemia was the fourth most common adverse event affecting 17.9% of the patients [37]. Similarly but with a lower percentage in the DUAL-1 and DUAL-2 study, in SSc patients treated with macitentan for the management of digital ulcers, anemia occurred in 5–11% of cases [38]. In addition, in a recent pilot study open-label trial in early diffuse systemic sclerosis 3/10 patients exposed to nilotinib, a tyrosine kinase inhibitor, showed anemia [39]. A recent report suggests that gemcitabine might induce an hemolytic uremic syndrome with accelerated hypertension, thrombocytopenia and Raynaud's phenomenon treated successfully with intravenous administration of a calcium channel blocker, oral administration of an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker plus transfusion of fresh frozen plasma [40].

Several studies support an increased risk of developing SRC with the use of steroids, and up to 60% of patients developing SRC had received steroids before the onset of this renal complication. Another case report linked the onset of scleroderma renal crisis with the use of a combination of tacrolimus and methylprednisolone [41]. Azathioprine is another drug that has been associated with a severe case of pure red cell aplastic anemia in systemic sclerosis patients and further supports a tight CBC monitoring if azathioprine therapy is needed for SSc patients [42].

Reports on cyclosporine use in SSc are contradictory: while some cases of aplastic anemia responded well to anti-thymocyte globulin [43] in association with cyclosporine, this medication was also linked to the development of uremic haemolytic syndrome with anemia and thrombocytopenia [44, 45].

Cases of haemolytic anemia in SSc patients has been reported also with the use of cyclofenil [46]. Of note, some medications have been directly linked to the onset of an immune thrombocytopenia: (1) the ingestion of L-tryptophan [47], used as a muscle-building adjuvant, (2) D-penicillamine [48] and (3) diclofenac [49] therapy have been all associated with an anti-platelet positive IgG immune thrombocytopenia. A case of macrophage activation syndrome has been reported in a SSc patients treated with etanercept [50].

Bone Marrow Insufficiency

In some cases, anemia and thrombocytopenia can be a direct expression of bone marrow dysfunction and some case descriptions report the occurrence of aplastic anemia successfully treated with anti-thymocyte globulin [51]. In addition, it is important to underline that recent case reports suggest the possible occurrence of macrophage activation syndrome in systemic sclerosis [52, 53]. While relatively rare as an haemotologic complication, due to its high mortality rate, this complication should be put high on the differential. Positive outcomes have been reported with etoposide, but larger studies are needed (Table 3.1) [54].

Pregnancy/Post-Partum/Infancy

Isolated reports highlight the relevance of careful CBC monitoring in pregnant patients with SSc and the occurrence of anemia and/or thrombocytopenia further complicates the differential diagnosis [55]. A case of pregnancy-associated

Table 3.1 Causes of anemia and thrombocytopenia

Causes of anemia	Causes of thrombocytopenia
Nutritional deficits (iron, vitamin B12, folic acid)	Microangiopathic/haemolytic (SRC—TTP—HUS)
Microangiopathic/haemolytic (SRC—TTP—aHUS)	Immune (ITP)
Autoimmune (AIHA)	Drug-induced
Drug-induced	

References: [9, 10, 12, 15, 21, 30, 31, 37–51, 55]
SRC, scleroderma renal crisis; *TTP*, thrombotic thrombocytopenic purpura; *HUS*, haemolytic uremic syndrome; *ITP*, immune thrombotic purpura; *AIHA*, autoimmune haemolytic syndrome

thrombotic thrombocytopenic purpura in a patient with Raynaud's phenomenon and anti-centromere antibodies was successfully treated with plasma exchange and high-dose prednisolone and angiotensin-converting enzyme inhibitor [56]. Additionally, another case reported the occurrence of thrombocytopenia in a pregnant SSc patient with severe pre-eclampsia [57]. Unfortunately, a severe scleroderma case with onset at 6 months of life [58] with anemia, failure to thrive, recurrent diarrhea, and ascites has been reported as well as the association between localized scleroderma and thrombocytopenia in pediatric age [59].

Conflict of Interest GB-none relevant to this manuscript.
DEF-none relevant to this manuscript.

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