

Autoimmune cytopenias complicating hematopoietic cell transplantation

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Abstract

Immune cytopenias after allogeneic hematopoietic cell transplantation are rare, albeit increasingly recognized, complications. Autoimmune diseases are serious complications of HCT and include immune-mediated cytopenias i.e. autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP) and autoimmune neutropenia. Severe cytopenia is usually defined by decreases of hemoglobin concentration below 7 g/dL, of platelet count below 20 G/L, or of absolute granulocyte count below 0.5 G/L, and it is mediated by the presence of auto-antibodies. ITP occurring in combination with AIHA is known as Evans Syndrome. Immune dysregulation is caused by impaired immune reconstitution and/or loss of self-tolerance. Primary risk factors of autoimmune cytopenias include: peripheral blood or cord blood as a stem cell source, unrelated HCT, non-malignant disease, use of alemtuzumab, acute/chronic graft-versus-host disease (GvHD), cytomegalovirus reactivation, infections, and, in pediatric settings, conditioning omitting total body irradiation. Diagnosis of autoimmune cytopenia is challenging due to a broad differential diagnosis: primary or secondary graft failure, infections, GvHD, disease relapse, drug-induced side effects, transplant-associated thrombotic microangiopathy, ABO-incompatibility, or disseminated intravascular coagulation. Treatment should be tailored to the individual patient, and ranges from watchful waiting to aggressive management in life-threatening situations. Apart from specific treatment adjusted for specific cytopenia, supportive care should include transfusions of leukocyte-reduced and irradiated red blood cell concentrates or pathogen-reduced platelet concentrates; treatment of infections and GvHD; modification of immunosuppression; and supplementation with microelements. Autoimmune cytopenias are usually highly resistant to standard therapy and are associated with increased risks of high morbidity and mortality, particularly when coexisting with other post-transplant complications.

Key words: autoimmune hemolytic anemia, AIHA, immune thrombocytopenia, ITP, autoimmune neutropenia, AIN

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Introduction

Definition

Post-transplant autoimmune cytopenia can occur as a single lineage disorder or in combination with other cell lines [1]. Autoimmune diseases are serious complications occurring after hematopoietic cell transplantation (HCT),

including immune-mediated cytopenias: autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP) and autoimmune neutropenia (AIN) [2–5]. Severe cytopenia is usually defined by a decrease of hemoglobin concentration below 7 g/dL, of platelet count below 20 G/L, or of absolute granulocyte count below 0.5 G/L, and is mediated by the presence of auto-antibodies.

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ITP occurring in combination with AIHA is known as Evans syndrome.

Pathophysiology

These cytopenias largely develop due to immune dysregulation due to impaired immune reconstitution [6–8], loss of self-tolerance, inability of functional regulatory T cells (Tregs) to suppress auto-reactive T-cells and auto-reactive B-cells [9–12], and transfer of autoantibodies or autoreactive T-cells. It can be associated with graft-versus-host disease (GvHD) or infections as well as the use of drugs used in prophylaxis and/or treatment of these complications [4, 9, 10, 13].

Risk factors

Due to the heterogeneous patient populations analyzed in various studies, risk factors of post-transplant autoimmune cytopenias are not yet fully established. Primary risk factors include: peripheral blood stem cells or cord blood as a stem cell source, unrelated HCT, non-malignant disease, use of alemtuzumab, acute and chronic GvHD, cytomegalovirus (CMV) reactivation, infections, and in pediatric settings, conditioning omitting total body irradiation (TBI) [9, 10, 13–18].

Principles of diagnosis

Initial clinical symptoms and signs are typical for developing cytopenia, including anemia or thrombocytopenia or neutropenia. Diagnostics is usually difficult and challenging. In differential diagnosis, cytopenia needs to be distinguished from primary or secondary graft failure, infections, GvHD, disease relapse, drug-induced side effects, transplant-associated thrombotic microangiopathy (TA-TMA), ABO-incompatibility, and disseminated intravascular coagulation (DIC) [1].

General principles of management

Autoimmune cytopenias are usually highly resistant to standard therapy and are associated with increased risks of high morbidity and mortality, particularly when coexisting with other post-transplant complications such as infections or relapse [5]. Nevertheless, the outcome of immune cytopenias is slowly improving over the calendar years. Supportive care includes transfusions of leukocyte-reduced and irradiated red blood cell (RBC) concentrates or pathogen-reduced platelet concentrates. Successful treatment of infections and GvHD might be helpful in maintaining cytopenia. Modification of immunosuppression has to be balanced against an increased risk of GvHD or relapse. In cases of deficiency, supplementation with vitamin B12, folate or iron is necessary. Prophylactic anticoagulation due to increased risk of thromboembolic events should be taken into account [19–21].

Autoimmune hemolytic anemia (AIHA)

The most frequent causes of hemolysis after allogeneic-hematopoietic cell transplantation (allo-HCT) are donor-/recipient (D/R) ABO incompatibility, autoimmune hemolytic anemia (AIHA) and TA-TMA. Some diseases can increase the risk of hemolysis i.e. non-Hodgkin lymphoma, paroxysmal nocturnal hemoglobinuria, and sickle-cell disease. Drugs used in conditioning (fludarabine), or in treatment of infections or GvHD, can induce hemolytic anemia [22]. AIHA after allo-HCT occurs in 1–5% of patients a median 5–10 months on from the day of transplant, and can be presented as warm (wAIHA) or cold AIHA (cAIHA) [22].

Diagnosis of AIHA

Symptoms and signs include fatigue, pallor, icterus, dyspnea, and circulatory symptoms (in cases of cAIHA). Laboratory tests show increased reticulocytes, spherocytes in wAIHA, agglutinated RBC in cAIHA (while there is an absence of schistocytes in cAIHA), increased lactate dehydrogenase (LDH) and bilirubin, and decreased haptoglobin. Immune hematological examinations include direct antiglobulin test (DAT, Coombs test), cold agglutinin testing, elution and adsorption techniques [23].

Diagnosis of subtypes of AIHA

In warm AIHA: IgG auto-antibody, mostly against common blood group antigens (Rh, Rhesus antigens), positive Coombs test (DAT) shows presence of IgG or IgG+C3 complement on the surface of the RBCs.

In cold AIHA: IgM auto-antibody against blood group i/I, and positive Coombs test (DAT) with the presence of complement on the surface of the RBCs.

In mixed AIHA, there is combined wAIHA and cAIHA.

In atypical AIHA, DAT (Coombs test) is IgA- or IgM-driven, although this may be negative (Table I) [14].

Differential diagnosis

The following pathologies should be included: ABO incompatibility, TA-TMA, acute or chronic GvHD, infections causing marrow suppression, drug-induced myelosuppression, drug-induced immunological distraction, graft failure and relapse of primary disease [24].

ABO incompatibility should be considered as a primary differential diagnosis of hemolysis after allo-HCT, as it occurs in about 30–50% of patients [23]. ABO incompatibility can be associated with acute hemolysis and pure red cell aplasia (PRCA) in cases of major ABO incompatibility, or with passenger lymphocyte syndrome (PLS) in cases of minor ABO incompatibility. This phenomenon is not related to donor human leukocyte antigens (HLA) match, as there is an independent inheritance of ABO blood groups (chromosome 9) and HLA genes (chromosome 6). Diagnostic tests in cases of ABO incompatibility include DAT and titration

Table I. Diagnosis of autoimmune hemolytic anemia (AIHA)

	Warm AIHA (wAIHA)	Cold AIHA	Mixed AIHA	Atypical AIHA
Antibody specificity	IgG	IgM	IgG and IgM	IgA or IgM (in wAIHA)
DAT (monospecific DAT)	IgG ±C3	C3 ±IgM	IgG +C3 ±IgM	IgA or IgM, DAT negative

IgG – immunoglobulin G; IgM – immunoglobulin M [14]; DAT – direct antiglobulin test; C – complement

Table II. Differential diagnosis of post-transplant autoimmune-mediated [autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP)]

Differential diagnosis	ABO incompatibility	GvHD	Graft failure, relapse	Infections	TA-TMA
Symptoms and signs	Hemolysis; PRCA; PLS	Acute GvHD; chronic GvHD	Persistent cytopenia; symptoms of primary disease	Clinical symptoms and signs	Tissue microvascular injury (kidneys, lungs, brain, GI)
Diagnostics	DAT and elution techniques; isohemagglutinins; bone marrow	Clinical diagnosis; histology examination	CBC; chimerism; bone marrow	Microbiological testing, imaging	CBC (schistocytes); platelets (↓); proteinuria; sC5b-5 (↑)

GvHD – graft-versus-host disease; TA-TMA – transplantation-associated thrombotic microangiopathy; PRCA – pure red cell aplasia; PLS – passenger lymphocyte syndrome; GI – gastro-intestinal; DAT – direct antiglobulin test; CBC – cell blood count

of isohemagglutinins. Bone marrow biopsy can be useful (Table II) according to Baur et al. [1].

TA-TMA is usually difficult to diagnose. Its incidence ranges between 10–35% after allo-HCT, and it is associated with chronic organ injury and high mortality. Thrombocytopenia and hypotension are typical early signs of TA-TMA. TA-TMA is a multi-system disorder of endothelial injury and organ damage (mainly kidneys, gastro-intestinal tract, and lungs) that can be triggered by chemotherapy, irradiation, immunosuppressive agents, GvHD and infections. Dysregulation or activation of the complement system, including complement gene variants, is another possible mechanism. Diagnostic confirmations include presence of schistocytes in blood smear, thrombocytopenia, proteinuria, and increase of soluble sC5b-9 protein.

Treatment of AIHA

Treatment should be individualized depending on the disease course and underlying diagnosis, because of the higher relapse risk. In mild compensated forms of AIHA, close observation may be appropriate. However, AIHA after allo-HCT can be life-threatening and even fatal, and therefore in some patients early diagnosis and prompt intervention is mandatory. The principles of treatment derive from those of primary AIHA (Table III) [10, 14, 25–31].

Treatment of warm AIHA:

- In first line, steroids (prednisolone 1 mg/kg/day) combined with rituximab (375 mg/m²/week) and intravenous immunoglobulins (2 g/kg) are used. The first-line treatment can be repeated in non-responding patients;
- In second line, additional options involve plasma-cell directed therapies including daratumumab (16 mg/kg/

/week) or bortezomib (1.3 mg/m²/week) together with steroids and other immunosuppressive drugs, particularly in patients with malignant disease and high risk of relapse or transplanted patients in non-complete remission. Since response to rituximab, daratumumab or bortezomib may be achieved after several weeks, bridging with steroids is mandatory, although steroid tapering should be performed quickly;

- In third line, the first- and second-line options can be combined. Additionally, plasma exchange (TPE) can be considered. Due to a high risk of infectious and thrombotic complications, splenectomy is not an attractive option and should be delayed. New options include abatacept and sirolimus [9, 32].

Treatment of cold AIHA:

- First line treatment includes rituximab (375 mg/m²/week) or rituximab combined with bendamustine (90 mg/m²);
- For second line, eculizumab (600 mg/week) or bortezomib (1.3 mg/m²/week) are proposed;
- In third line, TPE can be considered in severe cAIHA. It has an immediate but transient effect.

Transfusions of RBCs should be carried out if necessary. Antibodies in wAIHA are usually directed against common blood group antigens, and so excluding anti-RBC allo-antibodies is time-consuming. Even with this approach, cross-matching is usually positive. In cAIHA, transfusions should be applied warm [25, 27, 33]. Supportive care includes hydration, transfusions, supplementation with vitamin B₁₂, folate, iron, and avoidance of cold exposure. There is an increased risk of thromboembolic complications [14, 25–27, 29].

Table III. Treatment of autoimmune hemolytic anemia (AIHA) after allogeneic hematopoietic cell transplantation

Treatment	wAIHA	cAIHA
First-line	Steroids ±rituximab ±IVIG	Rituximab ±bendamustine
Second-line	Daratumumab*	Eculizumab*
	Bortezomib*	Bortezomib*
	Immunosuppressive drugs	
Third-line	Combination of first- and second-line; therapeutic plasma exchange; splenectomy	Therapeutic plasma exchange (immediate but transient effect)
Supportive treatment	Transfusions (leukocyte-reduced and irradiated red cell concentrates) [sufficient to reach 6–8 g/dL]; hydration; folate	Avoid cold exposure; hydration; transfusions (leukocyte-reduced and irradiated red cell concentrates) (recommended: warmed transfusions and infusions); folate

*Off-label use [10, 14, 25–31]; wAIHA – warm AIHA; cAIHA – cold AIHA; IVIG – intravenous immunoglobulins

Immune thrombocytopenia

Diagnosis

ITP after allo-HCT occurs in 0.5–2% of patients. It is usually a diagnosis of exclusion. Typical symptoms and signs include bleeding. Laboratory tests usually show isolated thrombocytopenia, absence of schistocytes in blood smear, and increased LDH. Tests for infectious causes should include CMV, Epstein-Bárr virus (EBV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Coagulation tests are necessary if microangiopathy is suspected. Testing for antibodies against (human platelet antigen (HPA) and HLA are indicated only in selected patients [34].

Differential diagnosis

Differential diagnosis is similar to AIHA: graft failure, infections, GVHD, relapse, TA-TMA, and drug-induced side-effects (Table II). Additionally, DIC should be used in differential diagnosis of bleeding or/and thrombotic complications, although DIC is always secondary to the underlying condition, such as severe infections, malignancies or trauma.

Treatment of ITP

Essentially, treatment is based on that in primary immune thrombocytopenia. Treatment is aimed at preventing bleeding. A watch-and-wait strategy is advised in patients without severe thrombocytopenia.

- In first line, steroids, either prednisolone or dexamethasone, together with immunoglobulins and rituximab, are used (Table IV) [10, 34–37];
- In second line, thrombopoietin receptor agonists (eltrombopag or romiplostim);
- In third line, the first- and second-line treatments can be combined. The use of daratumumab is a new option. Splenectomy is a last resort and should be delayed as

far as possible due to increased risk of infections and thrombotic complications.

Supportive measures include platelet transfusions in life-threatening bleeding, and tranexamic acid. There is no platelet threshold value for treatment, and this can vary depending on age, comorbidities and other drugs used including anticoagulants [34].

Autoimmune neutropenia

Definition

AIN can be seen as an isolated phenomenon, or in association with autoimmune diseases, or as a secondary manifestation of infections, drugs, or malignancies. As a primary disease, it occurs most frequently in infants and young children, and is a relatively benign disorder. It can range from mild neutropenia [absolute neutrophil count (ANC); <1.0 G/L] to severe (ANC <0.5 G/L) and very severe or agranulocytosis (ANC <0.2 G/L) [5]. Monocytosis is common. Cell destruction is usually extravascular.

Diagnosis

Infections and fever feature in a typical clinical presentation. Laboratory work-up includes cell blood count and blood smear and possibly testing of antibodies with specificity of human neutrophil antigen (HNA). DAT usually has no practical value in the diagnosis of AIN [38].

Differential diagnosis

Differential diagnosis in a transplant setting is similar to AIHA and ITP: drugs, disease relapse, infections, graft failure, and GvHD.

Treatment

Granulocyte colony-stimulating factor should always be the first line of therapy, with steroids and/or IVIG as the second-line approach (Table V).

Table IV. Treatment of immune thrombocytopenia (ITP) after allogeneic hematopoietic cell transplantation

Treatment	ITP
First-line	Steroids (prednisolone or dexamethasone) ±IVIG ±rituximab*
Second-line	Thrombopoietin receptor agonist (eltrombopag, romiplostim)
Third-line	Combinations (first- and second-line); immunosuppressive drugs; daratumumab; splenectomy
Supportive treatment	Transfusions (irradiated or pathogen-reduced platelet concentrates); tranexamic acid

*Off-label use [10, 34–37]; IVIG – intravenous immunoglobulins

Table V. Treatment of autoimmune neutropenia (AIN) after allogeneic hematopoietic cell transplantation

Treatment	AIN
First-line	G-CSF
Second-line	Steroids ±IVIG; possibly rituximab
Third-line	
Supportive treatment	Antimicrobial prophylaxis; treatment of infections

G-CSF – granulocyte colony-stimulating factor; IVIG – intravenous immunoglobulins

Authors' contributions

All authors contributed to design of study, writing of manuscript, critical review, and final approval.

Conflict of interest

All authors have nothing to disclose with respect to this paper.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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