Review Article
Drug-induced megaloblastic, aplastic, and hemolytic anemias: current concepts of pathophysiology and treatment

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Abstract: Drugs can affect all types of blood cells and induce different disorders. Drug-induced anemias are potentially dangerous and have long been a risk of modern pharmacotherapy. Megaloblastic, aplastic and hemolytic anemias are the most common drug-induced anemias. The mechanisms of drug-induced anemia can be explained in terms of either direct immune reaction or drug or metabolite toxicity. A large number of very commonly used drugs have been reported to induce anemias. Early diagnosis and proper treatment of drug-induced anemias are crucial because of the seriousness of these disorders. Removal of the offending drug is the primary treatment for drug induced oxidative hemolytic anemia.

Keywords: Drug-induced anemia, megaloblastic anemia, aplastic anemia, hemolytic anemia

Introduction

Drug-induced anemia and other blood disorders are potentially dangerous and have long been a risk of modern pharmacotherapy. Drug-induced blood disorders appear to be rare and only few studies have demonstrated the epidemiology and actual incidence of these reactions [1]. According to the Berlin Case-Control Surveillance Study conducted from 2000 to 2009, drug-induced blood dyscrasias represented 30% of all cases [2-5]. Extensive lists of drugs that have been implicated in adverse blood disorders have been developed throughout the past decades. Numerous very commonly used drugs have been listed and this makes it difficult to determine the cause of any abnormality [1]. Drugs can affect any type of blood cells and induce different disorders. The effect of drugs on RBCs has been manifested by causing a number of different anemias. Megaloblastic anemia, aplastic anemia, hemolytic anemia, thrombocytopenia, and agranulocytosis are the most common drug-induced hematologic disorders. This review focuses on common types of drug-induced anemias and available treatments.

Drug-induced megaloblastic anemia

Megaloblastic anemia is a disease characterized by distinguished hematopoietic cell morphology and unproductive hematopoiesis [6]. Defective nucleoprotein synthesis resulting in the development of megaloblastic anemia was described for the first time more than 50 years ago by Victor Herbert [7]. Megaloblastic anemia has been attributed to both acquired (common) and congenital (uncommon) problems as reported by Thomas Addison in 1849. Megaloblastosis usually results from not only a deficiency of folic acid and/or vitamin B12 (cobalamin), but also from a metabolic deficiency. Moreover, altered synthesis of pyrimidines, purines, or protein may result in megaloblastosis [8].

Nuclear-cytoplasmic dissociation where the cytoplasm matures more normally while the nucleus remains immature in appearance represents the hallmark of megaloblastosis. This dissociation is a result of retarded DNA synthesis and is manifested in the bone marrow and other proliferating tissues by cells with a normal-appearing cytoplasm and a large nucleus with immature-appearing diffuse chromatin
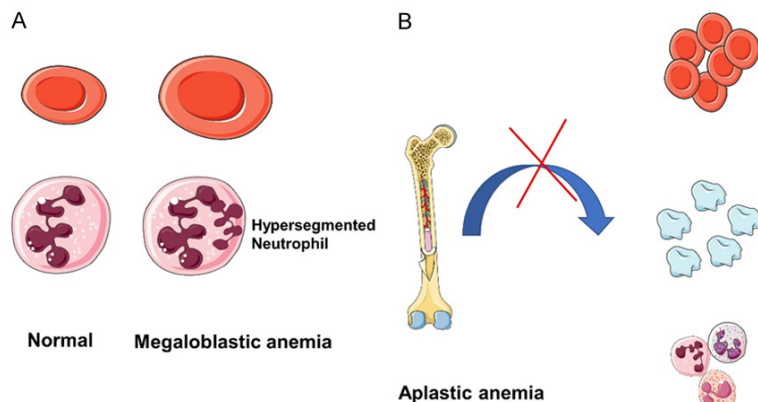
Figure 1. Megaloblastic and aplastic anemias.

(**Figure 1A**) [9]. It has also been reported that any abnormality in the replication process such as RNA synthesis, DNA assembly, or base precursor metabolism, can cause megaloblastosis [10]. Diagnosis of megaloblastic anemia must be made by measurement of folate and vitamin B12 levels because a high mean corpuscular volume does not necessarily imply megaloblastosis and some patients showed a normal-appearing cell line [10, 11].

Drugs has become a more prominent cause of megaloblastic anemia because most of the dietary causes of folate and vitamin B12 deficiency can be corrected [11]. Drugs that cause megaloblastosis are commonly used in clinical practice, but induced alterations in DNA synthesis pathways aren't always appreciated [11]. New synthesis of thymidine, a component of DNA but not RNA, is the most important biochemical process during DNA synthesis and hence is vulnerable to inhibition by drugs. The synthesis of thymidine occurs via methylation of pyrimidine which is folate and vitamin B12 dependent process [11]. Drugs cause megaloblastosis via physical destruction of the vitamins, competition for reducing enzymes, or by interfering with absorption, transport, or delivery of folate or vitamin B12 [8].

Antimetabolite chemotherapeutic agents are most frequently associated with drug-induced megaloblastic anemia due to their pharmacologic action on DNA replication. Several drugs are known to affect the activity of dihydrofolate reductase, an enzyme generating tetrahydrofolate for making deoxythymidine triphosphate, which is necessary for DNA synthesis. Drugs are known to have a low affinity to human dihydrofolate reductase, therefore, patients with adequate stores of folate or vitamin B12 are usually at low risk of developing drug-induced megaloblastosis [1]. One of the drugs causing megaloblastic anemia in 3-9% of patients is methotrexate [12]. Methotrexate is an irreversible inhibitor of dihydrofolate reductase that affects DNA synthesis [12].

Cotrimoxazole is another drug that has been reported to cause megaloblastic anemia with both low and high doses [13, 14]. Its effect is known to be more prominent in patients with folate or vitamin B12 deficiency [15]. Phenobarbital, primidone, and phenytoin have been implicated in drug-induced megaloblastic anemia. These drugs cause megaloblastosis through increasing folate catabolism or inhibiting folate absorption [1].

In general, drugs that cause megaloblastic anemia could be classified into different categories, including (1) drugs that alter purine metabolism, pyrimidine metabolism, or both, (2) drugs that interfere with absorption of folic acid, (3) inhibitors of ribonucleotide reductase, (4) drugs that interfere with the metabolism of folic acid and (5) drugs that decrease the absorption of vitamin B12 (**Table 1**).

Management and treatment of drug-induced megaloblastic anemia

To manage and treat drug-induced megaloblastic anemia, it is necessary to determine the cause of megaloblastosis. If there is an alternative, the causative agent might be discontinued and replaced by that alternative [11]. However, if the drug-induced megaloblastic anemia is related to chemotherapeutic agent, there would be no real therapeutic alternative and in this case the anemia becomes an acceptable side effect [1]. In this case, adequate intake of folate and vitamin B12 should be insured [11]. In addition, more awareness should be taken when agents that block DNA synthesis are used by physicians. Purine and pyrimidine analogues as well as folate antagonists are more potent

Table 1. Drugs that cause megaloblastic anemia [1, 11]

Mechanism of action	Drug/Agent	Class/Type/Indication of Medication
Drugs that decrease absorption of folic acid	Erythromycin	Antibiotic
	Aminosalicylic acid	For tuberculosis
	Nitrofurantoin	Urinary antiseptic
	Birth-control pills	Hormones
	Chloramphenicol	Antibiotic
	Ampicillin and other penicillins	Antibiotic
	Cotrimoxazole	Antibiotic
	Tetracyclines	Antibiotic
	Alcohol	In beverages
	Estrogens	Hormones
	Glutethimide	Hypnotic sedative
	Aminopterin	Antineoplastic and immunosuppressive
	Phenobarbital	Antiseizure
	Phenytoin	Antiseizure
	Sulfadoxine–pyrimethamine	Antimalarial
	Primaquine	Antimalarial
	Artemether lumefantrine	Antimalarial
	Chloroquine	Antimalarial
	Quinine	Antimalarial
Drugs that have folate analogue activity	Trimethoprim	Antimalarial
	Pyrimethamine	Antimalarial
	Raltitrexed	Antineoplastic
	Pemetrexed	Antineoplastic
	Proguanil	Antineoplastic
	Methotrexate	Antineoplastic and immunomodulator
Drugs that interfere with pyrimidine synthesis	Teriflunomide	Immunomodulator
	Leflunomide	Immunomodulator
	Cytosine arabinoside	Antineoplastic
	Methotrexate	Antineoplastic
	Gemcitabine	Antineoplastic
	Capecitabine	Antineoplastic
	Hydroxyurea	Antineoplastic
	Fluorouracil	Antineoplastic
	Mercaptopurine	Antineoplastic and immunomodulator
	Trimethoprim	Antibacterial
	Nitrous oxide	Anesthetic
	Leflunomide	Immunomodulator
Drugs that modulate purine metabolism	Mycophenolate mofetil	Immunomodulator
	Azathioprine	Immunomodulator
	Methotrexate	Immunomodulator and Antineoplastic
	Allopurinol	Xanthine oxidase inhibitor
	Pentostatin	Antineoplastic
	Fludarabine	Antineoplastic
	Cladribine	Antineoplastic
	Mercaptopurine	Antineoplastic
	Thioguanine	Antineoplastic
Drugs that decrease absorption of vitamin B12	Isoniazid	For tuberculosis
	Cycloserine	For tuberculosis and psychiatric conditions
	Aminosalicylic acid	For tuberculosis and inflammatory bowel disease
	Metformin	For diabetes and prediabetes
	Neomycin	Antibiotic
	Colchicine	For gout and familial Mediterranean fever
	Histamine2-receptor antagonists	H_2 blockers
	Proton-pump inhibitors	

Drugs that destroy vitamin B12	Nitric oxide
Drugs that increase excretion of vitamin B12	Sodium nitroprusside
Drugs that have unknown mechanism	Arsenic
	Sulfasalazine
	Asparaginase
	Benzene

and result in anemia that may occur very rapidly. Therefore, it is recommended to use less potent inhibitors and in this case megaloblastic anemia may develop more slowly [11]. In patients who receive cotrimoxazole, the induced megaloblastic anemia could be corrected via a trial course of 5-10 mg folinic acid up to four times a day [13, 14]. In addition, 1 mg/day folic acid can correct phenytoin- and phenobarbital-induced megaloblastic anemia, but may decrease the effectiveness of these medications [14].

Drug-induced aplastic anemia

Aplastic anemia (synonyms: panmyelopathy, panmyelophthisis) is a rare, serious disease of unclear etiology. It comprises a group of pathogenetically heterogeneous bone marrow failures and is characterized by a bi- or tricytopenia (thrombocytopenia, anemia and granulocytopenia) due to hypoplasia or aplasia of the bone marrow (**Figure 1B**) [16]. Aplastic anemia was first described during the autopsy of a pregnant woman after an episode of failed hematopoiesis [17]. Thereafter, several cases of aplastic anemia with uncertain incidence of the disease have been described [1]. Aplastic anemia can be classified into inherited and acquired categories. Inherited aplastic anemias include dyskeratosis congenita, Fanconi's anemia, and Diamond Blackfan anemia. These are inherited diseases that result in fatty infiltration and failure of bone marrow, and loss of circulating blood cells [18, 19].

Acquired aplastic anemia accounts for most cases and may result from viruses, chemical exposure, radiation, and drugs. Approximately 50% of aplastic anemia cases have been estimated to be acquired. However, in most cases the causative agent couldn't be precisely determined [18, 19]. In the 1930s, arsenicals and aminopyrines associated aplastic anemia was initially reported [20]. From a historical perspective, drug-induced aplastic anemias haven't been easily distinguished from idiopathic aplastic anemia [21].

Drug-induced aplastic anemia is the most serious acquired blood dyscrasia because of its associated high mortality which averages about 50% [22, 23]. In drug-induced aplastic anemia, multipotent hematopoietic stem cells undergo damage before their differentiation to committed stem cells [24]. Therefore, the number of circulating neutrophils, platelets, and erythrocytes is reduced [24]. Previous reports have showed that the incidence of drug-induced aplastic anemia is 2/million in Europe and North America which is two or three times greater in Asian countries. These findings point to the relationship between the risk and environmental factors [25, 26]. **Table 2** summarizes a list of drugs that induce aplastic anemia.

Symptoms of drug-induced aplastic anemia are of variable in onset. They may appear from days to months after initiation of the therapy with the causative drug [27]. Symptoms include fatigue, pallor, and weakness (signs of anemia), and pharyngitis, fever and chills (signs of neutropenia). Symptoms can also appear as neutropenia followed by thrombocytopenia after the discontinuation of the causative drug, [1, 27] while anemia develops slowly because of the longer life span of erythrocytes [28].

The pathogenic mechanism of drug-induced aplastic anemia includes the generation of intermediate metabolites that bind to DNA and proteins to cause bone marrow failure and toxicity on hematopoietic cells [29]. The variability in the presence of these metabolites as a result of genetic variation explains the idiosyncratic nature of drug-induced aplastic anemia [29]. The idiosyncratic drug-induced aplastic anemia is characterized by a latent period before the onset of anemia, continued bone marrow damage after drug discontinuation, and dose independence [29].

Table 2. Drugs that cause aplastic anemia [1]

Drug/Agent	Class/Type/Indication of medication
Carbamazepine	Antiseizure
Tocainide	Antiarrhythmic agent
Captopril	Antihypertensive
Chlorpromazine	Antipsychotic
Pentoxifylline	To treat muscle pain
Furosemide	A loop diuretic
Lithium	To treat the manic episodes of bipolar disorder
Oxyphenbutazone	Non-steroidal anti-inflammatory drug (NSAID)
Mebendazole	Antiparasitic
Phenothiazines	Antipsychotic
Penicillamine	To treat active rheumatoid arthritis and Wilson's disease
Thiazides	Antihypertensive
Nizatidine	A histamine H_2 receptor antagonist
Quinidine	Antiarrhythmic
Felbamate	Anticonvulsant
Interferon alfa	Antiviral and antitumor
Propylthiouracil	Anti-hyperthyroidism
Gold salts	Reduce inflammation in patients with rheumatoid arthritis
Sulindac	NSAID
Sulfonamides	Antimicrobial
Dapsone	Antibiotic
Methimazole	Anti-hyperthyroidism
Chlorothiazide	Antihypertensive
Acetazolamide	To treat open angle glaucoma
Lisinopril	Antihypertensive
Chloroquine	To treat malaria
Ticlopidine	Antiplatelet
Chloramphenicol	Antibiotic
Phenobarbital	Antiseizure
Phenytoin	Antiseizure

Young and Maciejewski have postulated direct toxicity, immune-mediated mechanisms, and metabolite-driven toxicity as the three major etiologies of drug-induced acquired aplastic anemia [24]. They have specified immune-mediated mechanisms as the most common cause of drug-induced aplastic anemia. In this immune reaction, exposure to drugs activates immune cells and production of cytokines, leading to the death of stem cells [24]. This hypothesis has been supported by laboratory studies showed improved *in vitro* colony formation when T lymphocytes were removed from patients with aplastic anemia [30]. Moreover, addition of these T lymphocytes to normal marrow inhibited *in vitro* hematopoiesis [30]. Furthermore, aplastic anemia patients who received anti-thymocyte globulin and cyclo-

phosphamide before allogeneic hematopoietic stem cell transplantation showed an improved hematopoiesis [31]. Another study conducted by Frickhofen et al. showed 65% improvement in platelets, RBCs, and WBCs counts in patients with severe aplastic anemia received anti-lymphocyte globulin, methylprednisolone, and cyclosporine as compared to 39% in the patients not receiving cyclosporine [32].

Management and treatment of drug-induced aplastic anemia

Aplastic anemia can be categorized depending on the blood counts into: moderate (neutrophils < 1,500 cells/mm³, platelets < 50,000 cells/mm³ and hemoglobin < 10 g/dL), severe (neutrophils < 500 cells/mm³, platelets < 20,000

Table 3. Drugs that induce oxidative hemolytic anemia [1]

Drug/Agent	Class/Type/Indication of medication
Sulfanilamide	Sulfonamide antibacterial
Nitrofurantoin	Antibiotic
Primaquine	Antimalarial
Phenazopyridine	Urinary tract analgesic
Sulfacetamide	Sulfonamide antibiotic
Sulfamethoxazole	Antibiotic
Metformin	Antidiabetic
Ascorbic acid	Vitamin
Rasburicase	To clear uric acid from the blood
Nalidixic acid	Antibacterial
Methylthioninium chloride	To treat methemoglobinemia
Dapsone	Antibiotic

cells/mm^3 and reticulocytes < 1%) and very severe aplastic anemia (neutrophils < 500 cells/mm^3, platelets < 20,000 cells/mm^3, reticulocytes < 1% and neutrophils < 200 cells/mm^3) [22, 24, 33]. For accurate diagnosis of aplastic anemia and to exclude other causes of pancytopenia, a bone marrow aspirate and biopsy is a necessity [34].

Treatment of aplastic anemia aims to limit the requirement for transfusions, improve peripheral blood counts, and minimize the risk for infections, and should be based on severity of the disease [1]. Because of the high mortality associated with drug-induced aplastic anemia, treatment should be initiated immediately after the anemia be diagnosed [1].

Removal or withdrawal of the causative agent of aplastic anemia is the first step in the treatment and may help in the disease reversal [1]. Treatment of moderate disease cases should be based on the degree of cytopenia and usually ranges from no clinical intervention to immunosuppressive therapy [21].

Basically, allogeneic hematopoietic stem cell transplantation and immunosuppressive therapy are the two major options for patients with drug-induced aplastic anemia. The therapy of choice depends on several factors, including disease severity, age and availability of a human leukocyte antigen-matched donor [21, 35].

Immunosuppressive therapy is the preferred first-line therapy for patients who are not candidates for allogeneic HSCT and for those older than 40 years [1]. Currently, the standard immunosuppressive therapy for aplastic ane-

mia is a combination of cyclosporine and anti-thymocyte globulin [36]. Cyclosporine inhibits activation of resting T cells via suppression of interleukin (IL)-2 production and release. Addition of cyclosporine to anti-thymocyte globulin improved failure-free survival, reduced the number of required immunosuppressive courses, and increased the response rate [37, 38]. This immunosuppressive regimen has been demonstrated to achieve 5-year survival rates, with a lower response in older patients [36].

Drug-induced hemolytic anemia

Hemolysis is the process of premature destruction of RBCs and can occur because of abnormal changes in the intravascular environment or defective RBCs. It has been postulated that drugs can induce hemolysis of RBCs via either mechanism [1]. Drug-induced hemolysis occurs intravascular or extravascular. Intravascular hemolysis can result from exogenous toxic factors, complement fixation to the RBC, or trauma [39]. On the other hand, extravascular hemolysis results from surface abnormalities on RBCs, leading to their phagocytosis in the spleen and liver [39]. Malaise, pallor, fatigue and shortness of breath represent the most common symptoms of drug-induced hemolytic anemia [1]. Because of the difficulty in assuring the specific causative agent and a clear diagnosis, the incidence of drug-induced hemolytic anemia can't be meticulously determined. It has been estimated that drug-induced hemolytic anemia has an incidence of 1/1-2 million [40].

Drug-induced hemolytic anemia can be categorized according to the causes into metabolic and immune hemolytic anemia. Metabolic hemolytic anemia is mediated by metabolic abnormalities in the patient's RBCs while immune hemolytic anemia results from the production of autoantibodies.

Drug-induced oxidative hemolytic anemia

Oxidative hemolytic anemia is a hereditary condition that can occur as a result of glucose-6-phosphate dehydrogenase (G6PD) deficiency [41]. Other deficiencies, including reduced glutathione peroxidase, methemoglobin reduc-

Table 4. Drugs that cause drug-induced immune hemolytic anemia [1]

Drug/Agent	Class/Type/Indication of medication
Angiotensin-converting enzyme inhibitors	To treat hypertension and congestive heart failure
Clavulanate	Antibiotic
Ciprofloxacin	Antibiotic
Interferon alfa	Antiviral and antitumor
Indinavir	To treat HIV/AIDS
Levodopa	To treat Parkinson's disease and Parkinson's-like symptoms
Lansoprazole	Proton pump inhibitor
Methyldopa	Antihypertensive
Minocycline	Antibiotic
Streptomycin	Antibiotic
Tazobactam	Antibiotic
Teicoplanin	Antibiotic
Tolbutamide	Potassium channel blocker
Tolmetin	NSAID
Triamterene	Diuretic
Sulbactam	β-lactamase inhibitor
Tacrolimus	Immunosuppressive
Rifampin	Antibiotic
Cefotetan	Antibiotic
Ceftriaxone	Antibiotic
Quinidine	Antiarrhythmic
Cladribine	Antineoplastic
Sulfonamides	Antimicrobial
Procainamide	Antiarrhythmic
Probenecid	Increases uric acid excretion
Rifabutin	Antibiotic
Omeprazole	To treat gastroesophageal reflux disease
Phenazopyridine	Urinary tract analgesic
Erythromycin	Antibiotic
Hydrochlorothiazide	Diuretic
Ketoconazole	Antifungal
Fludarabine	Chemotherapy
Levofloxacin	Antibiotic
Acetaminophen	Analgesic
Phenobarbital	Antiseizure
Phenytoin	Antiseizure

tase, or nicotinamide adenine dinucleotide phosphate (NADPH) have also been reported as causes of oxidative hemolytic anemia [41].

Among all, deficiency G6PD has been reported to be the most common and affects millions of people [42]. In the RBCs, G6PD participates in the production of NADPH to keep glutathione in its reduced form. Glutathione peroxidase uses reduced glutathione as a substrate to prote-

ct RBCs from oxidative damage via removal of peroxides [41]. RBCs deficient in G6PD are thus vulnerable to oxidative damage and hemolysis resulting from oxidation of the sulfhydryl groups of hemoglobin mediated by oxidative drugs [41]. The degree of RBCs hemolysis depends on the amount of generated oxidative stress and severity of the enzyme deficiency [41, 43]. **Table 3** summarizes a list of drugs that induce oxidative hemolytic anemia.
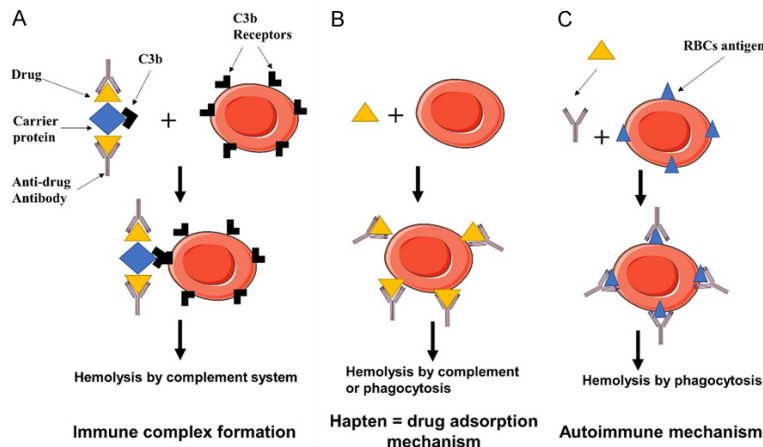
Figure 2. Mechanisms of drug-induced immune hemolytic anemia.

dent or independent. Drug-dependent antibodies are the more common form that only react in the presence of drug and causing hemolysis of RBCs [46]. To illustrate how drugs can induce immune hemolytic anemia, four pathogenic mechanisms have been proposed [47]. These mechanisms are innocent bystander, nonimmunologic protein adsorption to RBC membranes, hapten mechanism, and a mechanism involves the production of true RBC autoantibodies. **Table 4** summarizes a list of drugs that induce immune hemolytic anemia.

Treatment and management of drug-induced oxidative hemolytic anemia

In cases of drug-induced oxidative hemolytic anemia, the only available treatment is removal of the offending drug. It is strongly advisable to avoid drugs capable of inducing oxidative-mediated hemolysis in patients with enzyme deficiencies that can lead to drug-induced oxidative hemolytic anemia [1].

Removal of the offending drug is the primary treatment for drug induced oxidative hemolytic anemia. No other therapy is usually necessary because most cases of drug-induced oxidative hemolytic anemia are mild in severity. Patients with these enzyme deficiencies should be advised to avoid medications capable of inducing the hemolysis.

Drug-induced immune hemolytic anemia

Drug-induced immune hemolytic anemia has been estimated to occur in approximately 1-4/million/year [3]. It is a rare complication of drugs in which immunoglobulin M (IgM) or IgG binds to the surface of RBCs and initiates hemolysis through mononuclear phagocytic cells or the complement system [44]. Arndt reported that more than 130 drugs are associated with the development of drug-induced immune hemolytic anemia [45]. The most common classes are platinum based chemotherapies and the second and third generation cephalosporins [45].

In drug-induced immune hemolytic anemia, developed antibodies are either drug-depen-

Innocent bystander = immune complex mechanism

In this mechanism, IgM binds drugs to form immune complex which attach to the surface of RBCs. This binding activates the complement system resulting in intravascular hemolysis (**Figure 2A**) [47]. To induce this reaction, only a small amount of drug is required and is diagnosed by a positive Coombs test result. This mechanism of drug-induced immune hemolytic anemia is associated with acute intravascular hemolysis which may ultimately lead to hemoglobinuria and renal failure. Hemolysis can be stopped only after removal of the causative drug and confirmed by a negative Coombs test result [47].

Nonimmunologic protein adsorption to RBC membranes

This type of drug-induced immune hemolytic anemia has been associated with the use of β-lactamase inhibitors, [48] cisplatin, and oxaliplatin [49]. This mechanism is called membrane modification mechanism in which drugs induce changes in the RBCs membrane in the way that proteins attach to the cell. In this case, a positive antiglobulin test result is observed [48].

Hapten = drug adsorption mechanism

This mechanism of drug-induced immune hemolytic anemia has been reported in patients

who received high doses of penicillin and cephalosporin derivatives. Cefotetan and ceftriaxone are the most common cephalosporins that cause drug-induced immune hemolytic anemia via the drug adsorption mechanism [46]. Streptomycin and minocycline tolbutamide are other drugs reported to cause drug-induced immune hemolytic anemia through the hapten mechanism [43, 50].

In this mechanism, antibodies are developed against a stable complex of the administered drug with some soluble noncellular protein or molecule. Immune complexes of drug-anti-drug are formed upon further drug administration (**Figure 2B**). These complexes attach to the surface of RBCs and leading to their destruction via complement activation [47, 51]. Anemia of this type is known to develop in 7 to 10 days and could be reversed after 2 week of drug discontinuation [47, 51].

Production of true RBC autoantibodies = autoimmune mechanism

The anti-hypertensive drug methyldopa was the first known drug associated with production of true autoantibodies attacking RBCs and causing hemolysis [51, 52]. The mechanism of methyldopa-induced production of true RBC autoantibodies is not fully understood [52]. One suggested hypothesis states that methyldopa binds to immature RBCs, alter the RBCs membrane antigen, and induce the formation of true RBC autoantibodies. Another hypothesis suggests an impairment of immune tolerance induced by methyldopa or its metabolites (**Figure 2C**) [52]. Other drugs associated with the production of true RBC autoantibodies and subsequent hemolysis of RBCs are cladribine and fludarabine [1].

Treatment and management of drug-induced immune hemolytic anemia

Drug-induced immune hemolytic anemia may develop slowly or have a fulminant onset. Drugs that induce immune hemolytic anemia through the autoimmune or hapten mechanisms cause a slower hemolysis and the disease is mild to moderate in severity. On the other hand, drugs working through the immune complex mechanism can induce a sudden onset, severe hemolysis and may lead to renal failure

[1]. There are only a few prospective phase II trials [53-57] and a randomized study [58] for the treatment of drug-induced immune hemolytic anemia. Therefore, treatment is still not evidence-based.

The first option for the treatment of drug-induced immune hemolytic anemia is removal of the causative agent and providing a supportive care. Glucocorticoids can be helpful in severe cases of drug-induced immune hemolytic anemia [59]. Although IgG and rituximab (chimeric anti-CD20 monoclonal antibody) have been used in the treatment of drug-induced immune hemolytic anemia, their exact role is still not clearly defined [60, 61].

Concluding remarks and recommendations

Megaloblastic anemia, aplastic anemia, and hemolytic anemia are the most common drug-induced anemias. The mechanisms of drug-induced anemia can be explained in terms of either direct immune reaction or drug or metabolite toxicity. It is difficult to determine the exact cause of any drug-induced blood abnormality because of the large number of very commonly used drugs reported to induce blood dyscrasias. The usually applied method to establish the incidence of drug-induced adverse blood reactions is reporting during post-marketing surveillance.

Removal or withdrawal of the causative agent of drug-induced anemia is the first step in the treatment of drug-induced anemia and symptomatic support of the patient. This might help in the disease reversal. Because drug-induced anemias are potentially dangerous, more awareness should be taken when agents that blocks DNA synthesis are come into use by physicians. This can help avoiding the occurrence of megaloblastic anemia.

Drug-induced aplastic anemia is associated with high mortality; therefore, treatment should be initiated immediately after the anemia be diagnosed. Allogeneic hematopoietic stem cell transplantation and immunosuppressive therapy are the two major options for patients with drug-induced aplastic anemia. Immunosuppressive therapy is the preferred first-line therapy for patients who are not candidates for allogeneic hematopoietic stem cell transplantation and for those older than 40 years.

Patients with G6PD deficiency should avoid medications capable of inducing RBCs hemolysis. In cases of drug-induced oxidative hemolytic anemia, the only available treatment is the removal of the offending drug.

The first option for the treatment of drug-induced immune hemolytic anemia is removal of the causative agent and providing a supportive care. Glucocorticoids can be helpful in severe cases of drug-induced immune hemolytic anemia.

Disclosure of conflict of interest

None.

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