REPORT

Drug-induced immune neutropenia/ agranulocytosis

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Neutrophils are the most abundant white blood cell in blood and play a critical role in preventing infections as part of the innate immune system. Reduction in neutrophils below an absolute count of 500 cells/μL is termed severe neutropenia or agranulocytosis. Drug-induced immune neutropenia (DIIN) occurs when drug-dependent antibodies form against neutrophil membrane glycoproteins and cause neutrophil destruction. Affected patients have fever, chills, and infections; severe infections left untreated can result in death. Treatment with granulocyte colony-stimulating factor can hasten neutrophil recovery. Cumulative data show that severe neutropenia or agranulocytosis associated with exposure to nonchemotherapy drugs ranges from approximately 1.6 to 15.4 cases per million population per year. Drugs most often associated with neutropenia or agranulocytosis include dipyrone, diclofenac, ticlopidine, calcium dobesilate, spironolactone, antithyroid drugs (e.g., propylthiouracil), carbamazepine, sulfamethoxazole-trimethoprim, β-lactam antibiotics, clozapine, levamisole, and vancomycin. Assays used for detection of neutrophil drug-dependent antibodies (DDAbs) include flow cytometry, monoclonal antibody immobilization of granulocyte antigens, enzyme-linked immunosorbent assay, immunoblotting, granulocyte agglutination, and granulocytotoxicity. However, testing for neutrophil DDAbs is rarely performed owing to its complexity and lack of availability. Mechanisms proposed for DIIN have not been rigorously studied, but those that have been studied include drug- or hapten-induced antibody formation and autoantibody production against drug metabolite or protein adducts covalently attached to neutrophil membrane proteins. This review will address acute, severe neutropenia caused by neutrophil-reactive antibodies induced by nonchemotherapy drugs—DIIN. ***Immunohematology* 2014;30:95–101.**

Key Words: drug-dependent neutrophil antibodies, drug-induced immune neutropenia, agranulocytosis

Drug-Induced Immune Neutropenia

Neutrophils (polymorphonuclear leukocytes [PMNs]) are a type of granulocyte and are the major class of white blood cells (WBCs) in human peripheral blood. The circulation of a healthy human adult contains 4500 to 10,000 WBCs/μL with approximately 60 percent or more being neutrophils.[1] A healthy adult produces 1×10^{11} neutrophils each day, each of which survives about 6 to 8 hours in the circulation.[2] Neutrophils play an important role in the innate immune response and are critical to host defense against infectious disease. They circulate in the blood until recruited by chemical signals to sites of infection, where they function as phagocytes that engulf and kill extracellular pathogens with their microbicidal arsenal. Macrophages also contribute significantly to this process. Because of their important role in preventing infections, disorders that result in a significant lack of neutrophils put the host at risk of severe illness and even death. A reduction of neutrophils (segmented and band cells) in the blood circulation to less than an absolute neutrophil count (ANC) of 1000 to 1500/μL is considered neutropenia. An ANC less than 500/μL is considered severe neutropenia or agranulocytosis, and individuals with an ANC less than 100/μL are at severe risk of morbidity and mortality from infections.[3,4] The terms "agranulocytosis" and "neutropenia" are often used interchangeably, but some argue that use of the term "agranulocytosis" should be reserved for conditions in which the bone marrow cannot make sufficient granulocytes, and "neutropenia" when just neutrophils fall below normal levels.[5] For the purposes of this review, the terms will be used synonymously, with agranulocytosis representing cases of severe neutropenia in which the ANC is less than 100/μL.

Like thrombocytopenia and anemia, neutropenia can be induced after exposure to myriad drugs[6] and results from either decreased production or increased destruction of neutrophils. Decreased production is usually a consequence of exposure to chemotherapeutic drugs causing immune suppression of bone marrow myeloid precursors. Idiosyncratic or acute neutropenia resulting from increased neutrophil destruction is commonly caused by adverse reactions to nonchemotherapy drugs.[3,4,7]

Clinical Features, Diagnosis, and Treatment

Drug-induced immune neutropenia (DIIN) is typically suspected when a sudden severe drop in neutrophils (ANC <500/μL) occurs shortly after repeat exposure to a drug or 5 to 7 days after first exposure. Patients' symptoms include, but are not limited to, fever, chills, nonspecific sore throat, and myalgia or arthralgia. Diagnosis is difficult because patients often are asymptomatic before severe neutropenia

is discovered, usually from a blood count performed for another reason.[8] Without treatment, patients can experience severe infections, septicemia, and septic shock that can lead to death in 2 to 10 percent of cases.[4,7] In DIIN, the bone marrow typically shows normal or mild hypocellularity with decreased or absent myeloid precursor cells, or it can be hypercellular with neutrophilic maturation arrest.[8]

Criteria for drug imputability are the same as those applied in drug-induced immune thrombocytopenia or anemia: (1) exposure to the candidate drug preceded neutropenia, (2) recovery from neutropenia was complete and sustained after discontinuing candidate drug, (3) candidate drug was the only drug used before the onset of neutropenia or other drugs were continued or reintroduced after discontinuation of candidate drug with a sustained neutrophil count, and (4) other causes of neutropenia were excluded.

Treatment of patients with DIIN begins with immediate withdrawal of the implicated drug. Further treatment consists of supportive care for complications such as fever and infections, which may include analgesics and antibiotics for severe infections (ANC <100/μL) and antifungal agents for fungal infections. Treatment with recombinant granulocyte colony-stimulating factor (G-CSF) in severe infections can hasten neutrophil recovery and shorten neutropenic fever, but is more often used in neutropenia induced by chemotherapy.[4,7,9] Granulocyte transfusions are typically not required in DIIN, and the risk–benefit is not favorable.[9]

Incidence and Drugs Most Frequently Implicated

In 1980, the International Agranulocytosis and Aplastic Anemia Study (IAAAS), a population-based case-controlled surveillance program, was coordinated, which involved Israel and seven regions of Europe.[10] The most recent analysis of these data shows that the frequency of agranulocytosis in patients receiving nonchemotherapy drugs is approximately 5 cases/million population per year.[11] Cumulative data from IAAAS, case reports, and clinical trials show that agranulocytosis associated with drug exposure ranges from approximately 1.6 to 15.4 cases per million population per year.[4,7,9,11–13] Drug-associated neutropenia frequency increases with age, being highest in people older than 65 years, and the incidence is also higher in women.[11] Drugs most often associated with neutropenia include dipyrone (metamizole), diclofenac, ticlopidine, calcium dobesilate, spironolactone, antithyroid drugs (e.g., propylthiouracil), carbamazepine, quinine, sulfamethoxazole-trimethoprim, β-lactam antibiotics, clozapine, levamisole, and vancomycin (Table 1).[11,14] Neutropenia incidence is higher for a select number of drugs.

Propylthiouracil is used to treat hyperthyroidism (Graves disease) by decreasing the levels of thyroid hormone. Mild leukopenia (WBCs <4000/μL) occurs in 12 percent of adults and 25 percent of children receiving proplylthiouracil,[15] but severe neutropenia occurs less frequently (0.31%).[16]

A careful review of a 7-year period of 114 patients receiving home intravenous vancomycin therapy in New Mexico found 12 percent developed vancomycin-induced neutropenia and 3.5 percent had drops in ANC to 500/μL or less.[17]

The anthelmintic agent levamisole has been known to cause agranulocytosis or neutropenia in exposed patients since the 1970s,[18] primarily in individuals using cocaine adulterated with levamisole,[19,20] but also when used as adjuvant chemotherapy in patients with colorectal cancer.[21] Drug Enforcement Administration (DEA) reports in 2009 showed 69 percent of seized cocaine was contaminated with as much as 10 percent levamisole.[22] Neutropenia has been reported to occur in as many as 13 percent of patients exposed to levamisole.[22] In cancer trials, agranulocytosis associated with levamisole showed dose dependence, with agranulocytosis developing in 3.1 percent of patients receiving 2.5 mg/kg for 2 consecutive days every week compared with 0.1 percent receiving the same dosage for 3 consecutive days but every other week.[22]

Clozapine-induce neutropenia occurs in about 1 percent of patients during the first 3 months of treatment.[3] Clozapine, a dibenzodiazepine, is an atypical antipsychotic medication used in the treatment of schizophrenia resistant to conventional neuroleptics. Clozapine is perhaps the drug most often associated with agranulocytosis or neutropenia, and it carries five black box warnings alerting physicians to that risk and several other adverse effects of the drug. However, the mechanism responsible for severe neutropenia after exposure to clozapine is not immune mediated, but is the result of ATP depletion through formation of an active nitrenium metabolite that causes apoptotic destruction of neutrophils.[5,23]

Whereas the overall incidence of drug-induced neutropenia or agranulocytosis has been examined, the incidence of specifically DIIN is not well defined. This is primarily related to the difficulty in distinguishing drug-induced neutropenia caused by myelosuppression and direct neutrophil cytotoxicity from immune mechanisms, and poor sensitivity and availability of laboratory testing for detection of drug-dependent neutrophil antibodies.[8] Table 1 lists those drugs that have most often been reported to cause DIIN.

Table 1. Nonchemotherapy drugs reported to be associated with drug-induced neutropenia

Stroncek et al.[8]*	Berliner et al.[14]†	Tesfa et al.[5]†	BloodCenter of Wisconsin‡
aminopyrine	carbamazepine	alimemazine	cefepime
aminosalicylic acid	carbimazole	calcium dobesilate	ceftriaxone
amodiaquine	cephalosporins	cefepime	ciprofloxacin
amoxicillin	chloramphenicol	clozapine	clindamycin
ampicillin	methimazole	etanercept	ibuprofen
aprindine	penicillins	fluconazole	levetiracetam
carbimazole	sulfonamides	furosemide	piperacillin-tazobactam
cefotaxime	thiouracil	infliximab	quetiapine
ceftazidime	valproic acid	IVIG	sulfamethoxazole-trimethoprim
cefuroxime		ketoconazole	tacrolimus
cephradine		lamotrigine	vancomycin
chloral hydrate		mianserin	venlafaxine
chlorpropamide		metamizole	
chloroquine		methimazole	
clozapine		olanzapine	
dicloxacillin		pyrithyldione	
diclofenac		quinidine	
dimethyl aminophenazone		quinine	
flecainide		rifampicin	
gold thiomalate		rituximab	
Ibuprofen		rituximab	
levamisole		spironolactone	
mercuhydrin		sulfamethoxazole-trimethoprim	
methimazole		sulfasalazine	
nafcillin		triazole metamizole	
oxacillin		ticlopidine	
penicillin		vancomycin	
phenytoin		zidovudine	
procainamide			
propyphenazone			
propylthiouracil			
quinidine			
quinine			
sulfapyridine			
sulfathiazole			
sulfafurazole			

*Drugs reported to be associated with drug-induced immune neutropenia.

†Drugs reported to be highly associated with agranulocytosis.

‡Drugs in 2012 for which sera from patients with suspicion of drug-induced immune neutropenia were tested for antibodies in a flow cytometry assay by Platelet & Neutrophil Immunology Lab, BloodCenter of Wisconsin, Milwaukee. No drug-dependent antibodies involving these drugs were detected in any of the patients' sera.

IVIG = intravenous immunoglobulin G.

Laboratory Testing for Drug-Dependent Neutrophil Antibodies

As just mentioned, unlike for drug-induced immune thrombocytopenia and anemia, laboratory testing for neutrophil drug-dependent antibodies (DDAbs) is not as productive, and testing for neutrophil antibodies is not widely available. The reasons for this are that neutrophil antibody testing is technically complex, labor-intensive, and expensive. In addition, the inability to maintain the integrity of neutrophils

for testing by storage at 4°C or by cryopreservation requires that cells be isolated from fresh blood each day. This demands the regular availability of large numbers of blood donors. For these reasons, it is critical that granulocyte antibody and antigen testing be performed by an experienced laboratory using appropriate controls. When neutrophil DDAb testing is performed, methods used are very similar to those used for testing of platelet DDAbs with substitution of freshly isolated neutrophils for platelets. A typical assay consists of incubation of isolated neutrophils with patient's serum in the presence or absence of the implicated drug, followed by washing of cells incubated with drug with washes containing drug and those not incubated with drug, just with buffer. Neutrophils are then incubated with fluorescent or enzyme-labeled anti-human immunoglobulin (Ig)G or anti-human IgM for detection of bound DDAbs. Flow cytometry for immunofluorescent detection of DDAbs (Fig. 1) and monoclonal antibody immobilization of granulocyte antigens (MAIGA) assay for enzyme-linked immunosorbent assay (ELISA) detection and determination of the neutrophil glycoproteins targeted by DDAbs are methods in current use.[20,24–27] Other methods that have been used are immunoblotting, granulocyte agglutination test (GAT), and granulocytotoxicity.[8] Despite the availability of these various methods, neutrophil DDAbs, with the exception of those induced by quinine,[8,25,26,28,29] are rarely detected. The paucity of neutrophil DDAbs detected suggests that currently used tests lack sensitivity or that mechanisms responsible for drug-induced neutropenia often do not involve antibody formation (see next section on Pathogenic Mechanisms).

Like some platelet and red blood cell DDAbs,[30,31] neutrophil DDAbs that can only be detected in the presence of drug metabolites have also been reported.[32] Another issue is that, in the small number of cases in which patient sera have been tested, often the sera were tested without the addition of drug so that only nondrug antibodies were detected. The presence of non-DDAbs in suspected cases of DIIN suggests a drug-induced autoantibody mechanism is responsible for the patient's neutropenia. In vitro assays demonstrating DDAbs that inhibit the growth of myeloid progenitor cells have also been reported.[33]

The neutrophil glycoprotein targets of DDAbs have not been well studied for most drugs. Stroncek et al.,[28] using immunoprecipitation, showed that a quinine-dependent antibody targeted the neutrophil-specific protein CD177 and another unidentified glycophosphatidylinositol-linked membrane glycoprotein. Meyer et al.[27] found a cefotaxime DDAb targeted CD11b and CD35 and a metamizole DDAb directed against CD16.

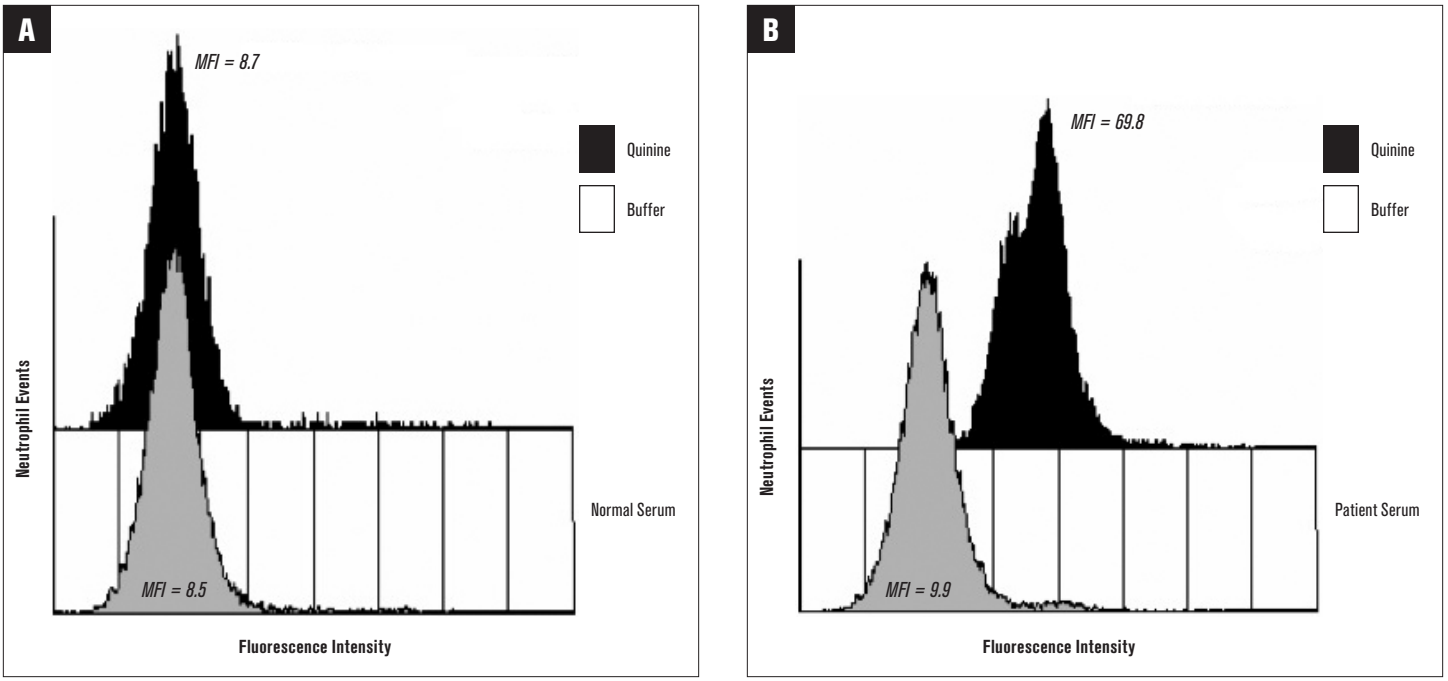

Fig. 1 Fluorescence histograms generated from immunofluorescence detection of immunoglobulin G (IgG) drug-dependent neutrophil antibodies by flow cytometry. Normal isolated neutrophils were incubated with sera and washed, and neutrophil-bound antibodies were detected with fluorescent anti-human IgG. **(A)** Normal serum incubated with neutrophils in the presence of either quinine (black histograms) or buffer (white histograms) shows low IgG fluorescence, indicating no antibodies are present. **(B)** Serum from a patient exposed to quinine with drug-induced neutropenia incubated with neutrophils showing high IgG fluorescence (MFI = 69.8) only with quinine, indicating the presence of quinine drug-dependent antibodies. Median fluorescence intensity (MFI) values are shown for each histogram.

Pathogenic Mechanisms

Mechanisms of drug-dependent antibody formation and binding to neutrophils have not been rigorously studied, and proposed mechanisms are largely unsubstantiated. However, some of the mechanisms proposed to explain DDAbs formed against platelets (see article in this issue of the journal) probably also apply to those against neutrophils, but this has not been proven. Greater study has been made of mechanisms to explain nonimmunologic drug-induced neutropenia or agranulocytosis. Proposed mechanisms of immunologic and nonimmunologic drug-induced neutropenia include oxidation of drugs by neutrophil reactive oxygen species (ROS), causing the formation of toxic metabolites or haptens, cytotoxicity by large granular T lymphocytes (T-LGL), disruptions of granulopoiesis and egress of neutrophils from the bone marrow, hapten- or drug-specific antibodies, formation of drug-induced autoantibodies, and genetic and epigenetic modifications that predispose an individual to drug sensitivity.[5,8] Mechanisms specific for DIIN will be discussed next.

Drug Oxidation

It is essential that drugs undergo biotransformation, primarily in the liver, into water-soluble metabolites that can be excreted in the urine to prevent cellular accumulation and toxicity.[34] Biotransformation gives rise to reactive intermediates and metabolites that can readily make covalent linkages with cellular proteins, including neutrophil membrane glycoproteins.[22] It is also possible that neutrophil enzymes such as myeloperoxidase (MPO) could be capable of producing reactive drug metabolites.[22] Once formed and attached to neutrophil proteins, these molecules could elicit drug-specific antibody production through a hapten mechanism or by production of autoantibodies targeting drug–protein adducts.[5,22] Several drugs associated with a significant incidence of agranulocytosis (e.g., methimazole,[22] propylthiouracil,[22] capatopril,[22] levamisole,[22] clozapine[5,22]) have been reported to form drug–protein adducts in vitro, although in contrast, structurally related drugs are rarely associated with agranulocytosis.[22]

Hapten Mechanism

Haptens are low-molecular-weight (usually <5000 daltons) molecules that are not capable of eliciting an immune response unless they are coupled to a larger carrier protein. Drugs like penicillin and some cephalosporin drugs when covalently linked to cell surface proteins can elicit drug-specific/hapten antibodies. This mechanism is well described for DDAbs targeting red blood cells (RBCs), which cause immune hemolytic anemia,[35] but has not been proven to occur in drug-induced thrombocytopenia.[36] As mentioned in the previous section, several drugs highly associated with agranulocytosis do form drug–protein adducts with neutrophil membrane glycoproteins that could elicit hapten-specific (drug-specific) antibodies that destroy neutrophils.[37] Hapten antibodies were reported to cause DIIN in patients exposed to flecanide[38] and dipyrone.[39]

Immune Complex Mechanism

Fc-receptors (FcR) are a family of related protein molecules expressed on various cells in the body that engage the Fc portion of immunoglobulins (antibodies) and regulate activation or inhibition of various cellular functions important in the immune response, including phagocytosis, immunoglobulin transport, and prevention of IgG catabolism.[40] Resting neutrophils express FcγRIIIb and FcγRIIa receptors and express FcγRI receptors when induced by various neutrophil-activating stimuli.[41] Therefore, neutrophils are capable of binding immune complexes of DDAbs and drug, but this mechanism has not been proven for DIIN.

Autoantibody Mechanism

Autoantibodies produced against platelets and RBCs have been reported after exposure to gold salts and α-methyldopa, respectively.[42] In some cases of suspected DIIN, neutrophil-reactive antibodies are detected that do not depend on the presence of drug.[20,43,44] It is possible that these non–drug-dependent antibodies could be true autoantibodies induced by the drug. Demonstration that serum from such patients reacts with autologous neutrophils collected once their ANCs normalize would be one way to confirm these are true autoantibodies, but there are no known reports in which such testing has been performed.

Summary

DIIN can occur in susceptible individuals 5 to 7 days after first exposure to a drug. Those affected typically experience acute, severe neutropenia or agranulocytosis (ANC <500/μL) and symptoms of fever, chills, sore throat, and muscle and joint pain. Although difficult to diagnosis, it is important to identify DIIN because, if left untreated, mortality is as high as 10 percent in cases exhibiting severe infections. Idiosyncratic drug-induced neutropenia or agranulocytosis occurs with a frequency of approximately 1.6 to 15.4 cases per million population per year, and is higher in the elderly and women.

The classes of drugs most commonly involved in DIIN include analgesics, antiarrhythmic agents, antibiotics, antimalarials, and antithyroid agents. Laboratory testing for neutrophil DDAbs as confirmation of DIIN is rarely performed owing to the difficulty and low sensitivity of tests used and the lack of testing availability. Flow cytometry, MAIGA, GAT, immunoblotting, and granulocyte cytotoxicity methods have been used to detect DDAbs. Some DDAbs target myeloid progenitor cells and cause neutropenia by inhibiting neutrophil production. Neutrophil glycoprotein targets that have been described for DDAbs include CD11b, CD16, CD35, and CD177. Mechanisms of drug-dependent antibody formation and binding to neutrophils have not been rigorously studied, and proposed mechanisms are largely unsubstantiated. Mechanisms that have been proposed include destruction of neutrophils by hapten/drug-specific antibodies, and auto-antibodies that bind adducts of drug metabolites bound to neutrophil membrane proteins formed after biotransformation of drugs, although several of the other mechanisms of drug-dependent antibody formation that have been described as causative of drug-induced immune thrombocytopenia could also possibly be involved in DIIN.

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