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Drug-Induced Agranulocytosis - Case Series

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SUMMARY

Introduction: Agranulocytosis is a life-threatening disorder characterized by disappearance of granulocytes from peripheral blood or decrease of peripheral neutrophil count below 0.5x10^9/l. It frequently occurs as idiosyncratic adverse drug reaction. It occurs especially in association with the use of antithyroid drugs, metamizole, aminopyrine and clozapine. The patients usually present with severe acute infections and sepsis. With modern management of broad-spectrum antibiotics and hematopoietic growth factors (G-CSF) the prognosis has been significantly improved.

Methods and results: We present 15 patients with drug-induced agranulocytosis, discuss the criteria for diagnosis, management and prognosis. Median patients age was 36 years (ranging from 25 to 61 years). The male/female ratio was 2/13. Underlying diseases were found in 10/15 (66.6%) patients, consisting of hyperthyreosis in 7 (46.6%) patients, mental disorders in 2 patients (13.3%) and in 1 (6.6%) patient suffering from perianal fistula. Nadir median neutrophil count was 0.3x10^9/l, range 0-0.5x10^9/l, hemoglobin was between 104 and 128 g/L, anaemia was present in 6 (54.5%) patients, platelet count was between 170 and 230x10^9/l. The treatment consisted of broad spectrum antibiotics, hematopoietic growth factor in 10, and antimycotic fluconazole in 3 patients. The outcome was favorable in 14 (93.3%) patients and 1 patient who had thyreotoxic crisis and agranulocytosis died. After 4 months, 1 (6.6%) patient, who had a complete recovery from agranulocytosis, developed an acute myeloid leukemia and died.

Conclusions: Drug-induced agranulocytosis is a rare haematological complication, with stable incidence and mortality rate of 5% to 10%. The responsible drug for agranulocytosis must be identified, discontinued and permanently contraindicated.

Keywords: agranulocytosis, idiosyncratic reaction, infection, hematopoietic growth factors

INTRODUCTION

Drug induced agranulocytosis (DIA), characterized by neutrophil count below 0.5x10^9/l, is a dangerous adverse reaction that can be caused by almost all classes of medicaments. The overall incidence of non chemotherapy DIA ranges from 2.6 to 10 cases per million patients exposed to drug per year [1]. Patients with such a severe neutropenia may initially

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be asymptomatic, although often proceed into severe life-threatening sepsis which can be fatal [2]. Medications such as antithyroid drugs, ticlopidine, clozapine, cotrimoxazole, are currently the typical causes of agranulocytosis. Clinical characteristics of patients with DIA are febrility, chills, oropharingeal infection with ulcerations and severe infections such as pneumonia and sepsis. With appropriate management, the mortality rate is currently estimated at 5–10% [3,4], but in elderly patients with comorbidities, the mortality rate can be still nowadays up to 20% [2,5].

We report our experience based on 15 patients with established criteria for agranulocytosis, who were treated with broad-spectrum antibiotic therapy and hematopoietic growth factors which helped survival of 14 patients.

METHODS AND RESULTS

In the study we analyzed clinical picture, laboratory data and outcome of 15 patients diagnosed with DIA at the Clinic of Hematology, Clinical Center Serbia in ten years period from 2006 to 2016 years.

Criteria for inclusion were neutrophil count below $0.5x10^9$/l, presence of fever and/or clinical signs of infection, onset of agranulocytosis during treatment or within 7 days in case of previous intake of the same drug and no clinical features and more than $1.5x10^9$/l neutrophils in blood cell count, 1 month after drug discontinuation [4,6]. The exclusion criteria were: existence of history of congenital neutropenia or immune neutropenia, no history of recent viral infection, suppression of bone marrow by recent chemotherapy, radiotherapy, and/or immunotherapy or development of an underlying hematological or malignant disease (infiltration of bone marrow with malignant cells) [6,7]. All 15 patients fulfilled the international criteria for DIA (4,5).

We examined the following data: age; gender; clinical features; medical history and co-morbidities; clinical presentation; causative drugs, Nadir of white blood cell; bone marrow analysis; time to reach a neutrophil count exceeding $1.5x10^9$/l (hematological recovery); use of hematopoietic growth factors (HGF), final outcome, and mortality rate. All patients had negative serological tests for human immunodeficiency virus, hepatitis B and C virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19.

Median age of the study group was 36 years (range 25–61 year). The male/female ratio was 2/13. Underlying diseases were found in 10 (66.6%), consisting of hyperthyreosis in 7 (46.6% patients), mental disorders in 2 patients (13.3%) and 1 (6.6%) patient suffering from perianal fistula who for pain relief was receiving metamizole as a causative drug for agranulocytosis. At admission the clinical presentation were isolated fever in 4 (26.6%) patients, documented pneumonia in 4 (26.6%), non systemic infections, sore throats and acute tonsillitis in 5 (33.3%) patients and a septic shock in 1 (6.6%) and 1 (6.6%) patient was asymptomatic. Bacteriological examination was positive in one patient (*Escherichia coli*), the other one had *Candida albicans* infection in oropharyngeal cavity. Nadir median neutrophil count was $0.3x10^9$/l, (range 0-$0.5x10^9$/l), hemoglobin level was between 104g/L and 128 g/L and anaemia was present in 6 (40.0%) patients, platelet count was normal, ranging between 170 and $230x10^9$/l. Bone marrow findings were available in all patients. Hypoplasia of granulocytic cells was found in 5 (33.3%) patients with cessation of myeloid precursor maturation, hyperplasia of granulocytic cells as sign of recovery in 5 (33.3%) patients, hypoplasia of granulocytic cells and megaloblas-

Definition of agranulocytosis:	Criteria of drug imputability
Neutrophil count <0.5 x 109/L ± existence of a fever and/or any signs of infection	Onset of agranulocytosis during treatment or within 7 days of exposure to the drug, with a complete recovery in neutrophil count of more than 1.5 x 109/L within one month of discontinuing the drug
	Recurrence of agranulocytosis upon re-exposure to the drug (this is rarely observed, as the high risk of mortality contra-indicates new administration of the drug)
	Exclusion criteria: history of congenital neutropenia or immune mediated neutropenia, recent infectious disease (particularly recent viral infection), recent chemotherapy and/or radiotherapy and/or immunotherapy* and existence of an underlying haematological disease

Table 1. Criteria for idiosyncratic drug-induced agranulocytosis [4-6]

tic erythroid changes in 1 (6.6%) and normal bone marrow finding in 4 (26.6%) patients.

The single causative drug was strengthened in 13 cases and in two patients two drugs were suspected as a cause. The distribution of causative drugs in this cohort of patients were as follow: antityreoid drugs tiamazol and propylthiouracil in 7 patients, metamizol in 2, clozapine in 2 and paracetamol in 2 patients, diclofenac and ibuprofen at the same time in 2 patients.

Before admission 8 (53.3%) patients were submitted to oral antibiotics but febrility continued in all.

After admission all patients were immediately given broad-spectrum parenteral antibiotics, often piperacillin or cefotaxime in association with vancomycin and 3 patients were given antimycotic diflucan. The median duration of antibiotic therapy was 8 days (range 4–20). No patient required blood transfusion. The median duration of hematological recovery (neutrophil count ≥1.5x10^9/l) was 8 days (range 4-15 days). G-CSF administered subcutaneously in a fixed dose of 300 μg/day, 48 h after DIA was diagnosed in 10 (66.6%) patients until the neutrophil count became over 1.5x10^9/l.

Clinical and laboratory characteristics of the patients are presented in Table 2.

Table 2. Characteristics of patients with DIA

Characteristic	Number of cases
Gender male/female	2 /13
Median age	36 (range 25-61)
Median neutrophil count nadir (range) x10^9/l	0.3 (range 0-0.5)
Median duration of agranulocytosis days	7 (4-15) days
Outcome	
recovery	14 (93.3%)
death	1 (6.6%)
Infection complications of agranulocytosis %	
Asymptomatic neutropenia	1 (6.6%)
Isolated fever	4 (26.6%)
Documented pneumonia	4 (26.6%)
Nonsystemic infections, sore throats and acute tonsillitis	5 (33.3%)
Sepsis	1 (6.6%)
Bone marrow examination %	
Normal	4 (26.6%)
Hypoplasia of granulocytic cells	5 (33.3%)
Hyperplasia of granulocytic cells	5 (33.3%)
Other abnormalities	1 (6.6%)
Medical history	
History of adverse drug rection	3 (20.0%)
Infection preceding acute agranulocytosis	1 (6.6%)
History of any allergic reaction	0
Causative drugs of agranulocytosis	
metamizole	2 (13.3%)
tiamazol	6 (40.0%)
propylthiouracil	1 (6.6%)
clozapine	2 (13.3%)
diclofenac, ibuprofen	2 (13.3%)
paracetamol	2 (13.3%)
Therapy for acute agranulocytosis	
antibiotics	15 (100%)
G-CSF	10 (66.6%)

The outcome was favorable in 14 patients. After 5 months 1 (9.09%) patient died from acute leukemia. This patient had perianal fistula and severe pain. He was given metamizole for pain relief after which he developed severe agranulocytosis. His white blood cell count was $0x10^9$/l. He was treated with broad spectrum antibiotics and G-CSF (which he received for 4 days). He completely recovered with normal white blood cells count but after 4 months he became malaise, he got haemorrhagic syndrome, febrility and on hematological survey an acute myeloid leukemia AML M2, *Flt3/ITD* +, *NPM* - was diagnosed. He died in aplasia 11 days after termination of induction chemotherapy.

DISCUSSION

DIA is extremely rare life-threating condition with annual incidence 3 to 16 cases per million population per year [2,6,7]. The number of fatal cases decreased during the last few decades. The main poor prognostic factors are: age over 65 years, neutrophil count at diagnosis of <0.1x109/l, development of severe septicemia and septic shock, as well as pre-existing comorbidities such as diabetes mellitus, cardiac failure and renal impairment [4,8].

The current definition of DIA is proposed by IAAAS and Benichu et al [6]. It is characterized by sudden onset and severe drop of neutrophil count below $0.5x10^9$/l. All our patients fulfilled criteria for agranulocytosis, with median neutrophil count of $0.4x10^9$/l with complete recovery of white blood cells and neutrophils in all 14 cases after removal of causative agent and the treatment [4-6]. The drugs that most frequently caused agranulocytosis were changing during the time, from aminopyrine, pirazolone, anti-thyroid drugs to sulfasalazine, phenothiazines, semi-synthetic penicillins, procainamid, non-steroidal anti-inflammatory drugs, aminopyrine derivatives, benzodiazepines, barbiturate, gold compounds, sulfonamides which are the most common causative agents of neutropenia and agranulocytosis in the world nowadays [9-13]. In our group of patients incriminated drugs were antithyroid medicaments, neuroleptics, analgetics, antipyretics and nonsteroidal anti-inflammatory agents.

The occurrence of agranulocytosis with the use of antithyreoid drugs was noticed soon after their introduction in the treatment of hyperthyreosis. The incidence of agranulocytosis cased by propylthiouracil, methimazole and carbimazole is 0.1-0.37% of patients receiving this medication per year [12]. Antithyroid drug agranulocytosis often occurs during the first 3 months of treatment, but it can occur even after a long period of treatment [10].

The mechanisms of neutropenia and agranulocytosis may be immune mediated or can be the result of direct damaging effect of used drug on granulocytic cell line [13]. It may occur as an idiosyncratic reaction, most often secondary through different mechanisms accelerating immune-mediated destruction. Some drugs act as haptens (aminopyrine, penicillin, gold compaunds) inducing antibody formation against neutrophils [13,14]. Circulating immune complexes may be formed and bind to neutrophils causing their destruction [13]. Clozapine is an example of drug which accelerates the process of apoptosis of neutrophils, not directly, but rather after bioactivation and formation of reactive nitrenium ion [15] which covalently binds to cellular proteins and induces neutrophil cell toxicity. Beta-lactam antibiotics at high concentrations induce inhibition of growth of colony-forming units of granulocytes and macrophages [16]. Ticlopidine acts over direct reversible cytotoxity for hemopoietic progenitor stem cells [17]. There are some drugs for which genetic risk factors have been recently identified. Genetic analysis of human leukocyte antigen genotyping and genome-wide association study in patients with antithyroid drug-induced agranulocytosis demonstrated presence of two independent susceptibility loci *HLA-B*38:02* and *HLA-DRB1*08:03* as the major genetic determinants of those patients [18]. In white European population, antithyroid drug-induced agranulocytosis was associated with HLA-B*27:05 and with other single nucleotide polymorphisms on chromosome 6. In the future, carriers of these variants could be offered alternative treatment for hyperthyroidism [19]. This results could be useful for antithyroid DIA and potentially for agranulocytosis caused by the other drugs.

The clinical characteristics of agranulocytosis in our cohort of patients was similar to other series [2,20]. Our patients had less severe infections, like septicemia, septic shock probably due to early antibiotic therapy before hospitalization. That might also be the reason that all our patients survived. It should also be

noted that our study group was young (median age 36 years) and without serious comorbidities like diabetes mellitus, rheumatic disease, cardiac failure or respiratory insufficiency.

The most common site of infections in DIA are mucous membranes, oral cavity, presenting as oral ulcerations, pharyngitis, ulceronecrotic pseudomembrane angina, oedema of regional lymph nodes and swelling. Manifestations of infection on the skin are rash, ulcerations and abscesses. Perirectal infection are also common. Systemic infections of lungs and genitourinary tract may be fatal if they spread to blood stream. A jaundice, as a sign of septic hepatitis, is a very serious complication announcing fatal outcome. But in modern time the treatment of infections as early as possible with broad spectrum antibiotics and G-CSF reduces the risk of fatal outcome. The pathogens causing infections are bacteria, but also fungi were increased in incidence in the last years. Infected patients may develop toxic shock with fever, hypotension, diffuse rash and respiratory distress syndrome with fatal outcome.

CONCLUSION

In conclusion, in the occurrence of neutropenia, febrility, and signs of inflammation during any drug treatment a DIA should be immediately considered. Any drug as a presumed causative agent should be discontinued for ever. Management of bacterial and fungal infections with broad spectrum antibiotics and hematopoietic growth factors may reduce mortality, enable complete hematological recovery and reduce days of hospitalization. A numerous medicaments are emerging as possible causative agents of DIA so that every medication should be closely followed up and in the case of neutropenia or DIA it must be removed for ever.

CONFLICTS OF INTEREST

The authors have no conflict of interest.

REFERENCES

1. Patton WN, Duffull SB. Idiosyncratic drug-induced haematological abnormalities. Incidence, pathogenesis, management and avoidance. Drug Saf, 1994; 11(6): 445-62. PMID:7727054

2. Andres E, Maloisel F, Kurtz JE, Kaltenbach G, et al. Modern managment of non - chemotherapy drug - induced agranulocytosis: A monocentric cohort study of 90 cases and review of the literature. Eur J Intern Med, 2002; 13: 324-8 PMID:12144912 doi. org/10.1016/S0953-6205(02)00085-7.

3. Palmblad J, Dufour C, Papadaki HA. How we diagnose neutropenia in the adult and elderly patient. Haematologica. 2014;99:1130-3. doi:10.3324/haematol.2014.110288

4. Andrès E, Cottet RM, Maloise F. Diagnosis and management of idiopathic drug-induced and severe neutropenia and agranulocytosis: What should the lung specialist know? J Lung Health & Dis (2018) 1(1): 31-38 PMID:28954408, DOI:10.3390/jcm6100092

5. Mourot-Cottet R, Maloisel F, Séverac F, Keller O, et al. Idiosyncratic Drug-Induced Severe Neutropenia and Agranulocytosis in Elderly Patients (≥75 years): A Monocentric Cohort Study of 61 Cases. Drugs - Real World Outcomes 2016,3; 393-9. PMID: 28160479 doi:10.1007/s40801-016-0091-4

6. Bénichou C, Solal-Celigny P. Standardization of definitions and criteria for causality assessment of adverse drug reactions. Drug-induced blood cytopenias: report of an international consensus meeting. Nouv Rev Fr Hematol. 1991;33:257-62. PMID:1956763

7. Kaufman DW, Kelly JP, Levy M, Shapiro S. The drug etiology of agranulocytosis: an update of the International Agranulocytosis and Aplastic Anemia Study. Pharmacoepidemiol Drug Safety 1993;2:525-9. DOI: 10.1002/pds.2630020706

8. Ibáñez L, Sabaté M, Ballarín E, Puig R, Vidal X, Laporte JR. The Agranulocytosis and Aplastic Anaemia Study Group of Barcelona. Use of granulocyte colony-stimulating factor (G-CSF) and outcome in patients with non-chemotherapy agranulocytosis. Pharmacoepidemiol Drug Safety 2008;17: 224-8. PMID:18181220 doi: 10.1002/pds.1542.

9. Andres E, Maloisel F , Zimmer J. The role of haematopoietic growth factors granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in the management of drug-induced agranulocytosis. Br J Haematol 2010;150:3-8. PMID:20151980 doi: 10.1111/j.1365-2141.2010.08104.x

10. Sun MT, Tsai ChH, Shih KCh. Antithyroid drug-induced agranulocytosis. Case report. J Chin Med Assoc 2009;72:438-41. PMID:19687001 doi: 10.1016/S1726-4901(09)70402-2.

11. Tamai H, Takaichi Y, Morita T, Komaki G, et al. Methimazole-induced agranulocytosis in Japanese patients with Graves' disease. Clin Endocrinol (Oxf)1989;30:525-30. PMID:2605789 doi: 10.1111/j.1365-2265.1989.tb01424.x

12. Nakamura H, Miyauchi A, Miyawaki N, Imagawa J. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. J Clin Endocrinol Metab 2013;98:4776-83. PMID:24057289 doi: 10.1210/jc.2013-2569.

13. Bhatt V, Saleem A. Review: drug-induced neutropenia-pathophysiology, clinical features, and management. Ann Clin Lab Sci 2004;34:131-7. PMID:15228223

14. Salama A, Schutz B, Kiefel V, et al. Immune mediated agranulocytosis related to drugs and their metabolites: mode of sensation and heterogeneity of antibodies. Br J Haematol 1989;72:127-32. PMID:2788011 doi: 10.1111/j.1365-2141.1989.tb07672.x

15. Williams DP, Pirmohamed M, Naisbitt DJ, et al. Induction of metabolism-dependent and –indipendent neutrophil apoptosis by clozapine. Mol Pharmacol 2000;58:207-16. PMID:10860943 doi: https://doi.org/10.1124/mol.58.1.207

16. Irvine AE, French A, Daly A, et al. Drug induced neutropenia due to direct effects on CFU-C. Ten years of culture experience. Eur J Haematol 1994;52:21-7.PMID: 8299766 DOI: 10.1111/j.1600-0609.1994.tb01280.

17. Symeonidis A, Kouaklis-Symeonidis A, Seimeni U, et al. Ticlopidine-induced aplastic anemia: two new case reports, review, and meta-analysis of 55 additional cases. Am J Hematol 2002;71:24-32. PMID:12221670 doi:10.1002/ajh.10150

18. Chen PL, Shih SR, Wang PW, Lin YCh, Chu CC, Lin JH et al. Genetic determinants of antithyroid drug-induced agranulocytosis by human leukocyte antigen genotyping and genome-wide association study. Nature Communication 2015; PMID:26151496doi:10.1038/ncomms8633

19. Hallberg P, Eriksson N, Ibañez L, Bondon-Guitton E, et al; EuDAC collaborators. Genetic variants associated with antithyroid drug-induced agranulocytosis: a genome-wide association study in a European population. Lancet Diabetes Endocrinol. 2016;4:507-16. PMID: 27157822 doi: 10.1016/S2213-8587(16)00113-3

20. Julia A, Olano M, Bueno J, Revilla E, et al. Drug-induced agranulocytosis: prognostic factors in a serie of 168 episodes. Br J Haematol 1991;79:366-72.PMID:1751364 doi: 10.1111/j.1365-2141.1991.tb08042.x

Agranulocitoza izazvana lekovima – serija slučajeva

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KRATAK SADRŽAJ

Uvod: Agranulocitoza je po život opasni poremećaj koji se karakteriše iščezavanjem granulocita iz periferne krvi ili smanjenjem broja neutrofila u perifernoj krvi ispod $0.5x10^9$/l. Obično se dešava kao idiosinkratična reakcija na lekove, naročito antitireoidne lekove, metamizol, aminopirin i klozapin. Akutna infekcija i sepsa su najčešći oblici kliničke prezentacije ove bolesti.
Metode i rezultati: Autori prikazuju 15 bolesnika sa agranulocitozom izazvanom lekovima i razmatraju kriterijume za postavljanje dijagnoze, lečenje i prognozu bolesti. Srednja starost naših bolesnika bila je 36 godina (raspon 25-61). Bila su 2 muškarca i 13 žena. Osnovna bolest postojala je kod 10/15 (66.6%) bolesnika i to, hipertireoza kod 7 (46.6%), mentalni poremećaji kod 2 (13.3%) bolesnika dok je 1 (6.6%) bolesnik bolovao od perianalne fistule. Srednji broj neutrofila bio je $0.3x10^9$/l, raspon $0\text{-}0.5x10^9$/l, hemoglobin je bio između 104 i 128 g/L, anemija je postojala kod 6 (40%) bolesnika a trombociti su se kretali između 170 i $230x10^9$/l. Lečenje se sastojalo u davanju antibiotika širokog spektra kod svih bolesnika, hematopoetskog faktora rasta kod 10, i antimikotika flukonazola kod 3 bolesnika. U 14 (93.3%) bolesnika postignut je kompletan oporavak a 1 bolesnica sa tireotoksičnom krizom i agranulocitozom je umrla. Posle 4 meseca 1 (6.6%) bolesnik, koji se inače potpuno oporavio od agranulocitoze, razvio je akutnu mijeloidnu leukemiju od koje je završio letalno.
Zaključak: Agranulocitoza izazvana lekovima je retka hematološka komplikacija sa stabilnom incidencom i smrtnošću od 5% do 10%. Lek odgovoran za agranulocitozu mora biti identifikovan i trajno uklonjen iz bilo kakve dalje terapije. Savremenim lečenjem antibioticima širokog spektra i hematopoetskim faktorom (G-CSF) prognoza bolesti je značajno poboljšana.

Ključne reči: agranulocitoza, idiosinkrazna reakcija, infekcija, hematopoetski faktori rasta

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