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Review Article

Drug-Induced Agranulocytosis: A Mini Review

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ABSTRACT

Agranulocytosis is also known to be granulopenia, causing neutropenia in circulating blood streams. The destruction of white blood cells takes place which leads to increase in the infection rate in an individual where immune system of the individual is suppressed. The symptoms includes fever, sore throat, mouth ulcers. These are commonly seen as adverse effects of a particular drug and are prescribed for the common diagnostic test for regular monitoring of complete blood count in an admitted patient. Drug-induced agranulocytosis remains a serious adverse event due to occurrence of severe sepsis with deep infection leading to pneumonia, septicaemia, and septic shock in two-third of the patient. Antibiotics seem to be the major causative weapon for this disorder. Certain drugs mainly anti-thyroid drugs, ticlopidine hydrochloride, spironolactone, clozapine, antiepileptic drugs (clozapine), non-steroidal anti-inflammatory agents, dipyron are the potential causes. Bone marrow insufficiency followed by destruction or limited proliferative bone marrow destruction takes place. Chemotherapy is rarely seen as a causative agent for this disorder. Genetic manipulation may also include as one of the reason. Agranulocytosis can be recovered within two weeks but the mortality and morbidity rate during the acute phase is seems to be high, appropriate adjuvant treatment with broad spectrum antibiotics are prerequisites for the management of complicated neutropenia. Drugs that are treated for this are expected to change as a resistant drug to the patient. The pathogenesis of agranulocytosis is not yet known. A comprehensive literature search has been carried out in PubMed, Google scholar and articles pertaining to drug-induced agranulocytosis were selected for review.

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INTRODUCTION:

Agranulocytosis is rarely seen idiosyncratic adverse reaction to a drug, which is potentially fatal. Drug induced agranulocytosis is characterised by decreased white blood cells causing neutropenia, in which the whole count of white blood cells is reduced to least count, rarely seen as zero in few patients [1,2]. The disorder occurrence takes place by the decrease in the immunity of an individual, where the patient couldn't resist the infections leading to severe consequences, and finally death [3]. Agranulocytosis usually manifests with a fever and sore throat. It is standard practice to advise patients about this side effect and to instruct them to stop the medication and seek urgent medical advice and a blood test, when they develop symptoms of agranulocytosis [4]. Over a past few years, the mortality rate has lowered, where the current level is at <5%, which can be explained partly by earlier recognition and the improved clinical management of associated intercurrent infections that may lead to severe sepsis if left untreated [5]. Although associated with many drugs, the side effect is rarely seen, only in few patients due to its safety and efficacy. The true impact of use of haematopoietic growth factors which includes granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), it is not evident about the death ratio [6]. Studies have shown that molecules such as

growth factor G-CSF reduce the disorder particularly in terms of antibiotic usage and length of hospital stay. Their use is particularly recommended for patients with poor prognostic factors, such as a neutrophil count less than $0.1 \times 10^9/l$, geriatric patients carrying severe infections. In such cases, that the drug causing agranulocytosis should be avoided which must remain contraindicated. The adjuvant management with regulatory agency must also be notified of the adverse event.

Drug-induced agranulocytosis is a serious adverse event due to the occurrence of deep infections which includes pneumonia, septicaemia, and septic shock in most patients. Geriatric patients greater than 65 years, disorders such as septicemia or shock and metabolic disorders such as renal failure, and a neutrophil count under $0.1 \times 10^9/l$ are poor prognostic factors. Appropriate adjuvant treatment with broad-spectrum antibiotic therapy and hematopoietic growth factors, the mortality rate is currently estimated around 5%.

The onset of agranulocytosis is generally concomitant with treatment. The course of agranulocytosis is of two types and consists of increasing severity through death from severe infection or recovery. First, it is characterised by sudden

lowering of leucocyte count in peripheral blood stream which is due to usage of antibiotics, on account of drug sensitivity, prototype of this type of reaction includes aminopyrine. The next mechanism includes formation of lupus like syndrome, and occurrence of leukopenia in result to sensitization to drugs like procainamide. In final step, development of Agranulocytosis takes place during which the patient is treated with chlorpromazine [7,8].

Causative reaction

Regarding causation, it is achieved only with toxic manifestation of drug over dosage. Relative certainty is possible if the drug produces leukopenia with over dose in an appropriate latent period. Thus leukopenia regularly occurs due to treatment with alkylating agents, folic acid antagonists which inhibit nucleic acid syntheses. The demonstration of measurable blood levels during reaction may contribute aetiological significance.

Clozapine induced agranulocytosis

Clozapine-induced agranulocytosis (CA) is quite complicated adverse drug adverse reaction. It is difficult to understand mechanism involved in this reaction. Clozapine (CLZ) provides effective treatment for schizophrenia; on the other hand, its usage is reduced due to causation of agranulocytosis. Use of clozapine as first-line drug thus denotes the biomarkers for drug-induced agranulocytosis [9,10]. Because of its binding to serotonergic, dopamine receptors it is classified as an atypical antipsychotic drug. The usage of clozapine has been reduced due to potential life-threatening adverse drug reaction, which includes agranulocytosis [11,12,13]. Blood testing for patients taking CLZ is recorded thus, clinical use of the drug is complicated. Clinical study have stated that the CLZ gives better result when it is used as 1st line drug than 3rd line drug based on its overall benefit/ risk ratio [14]. Olanzapine (OLZ) is analogue of CLZ, but has lesser effectiveness in treatment of schizophrenia. The chances of causing agranulocytosis is less when compared to CLZ [15,16,17]. Direct under medical supervision would help patients for whom this medication is the only hope of recovery. At the high risk of worsening the patient's mental illness, discontinuation of clozapine in their management is done, and relevant infection control procedures have been proceeded. Granulocyte-colony stimulating factor (G-CSF) is used for the restoration of the white cell line [18]. In first 6 months of treatment the highest risk of clozapine-induced agranulocytosis is seen and the ratio is higher in the initial 18 months after the onset of treatment [19]. The mechanism of clozapine-induced agranulocytosis is unclear whether clozapine or its major stable metabolites, N-desmethylclozapine at its therapeutic drug concentrations (1-3 µM), and is proved that it is cytotoxic to neutrophils or interferons directly, with change in the bone marrow precursor cells [20,21]. Clozapine-induced agranulocytosis is mostly seen in an immune-mediated mechanism or an immunological background, as on reuse of the drug, development of chronic phase takes place and reoccurrence of toxicity is faster [22]. Dose and serum level of clozapine does not cause clozapine-induced agranulocytosis although few reports have stated that -this could be dose related issue.

[23,24]. The phenomenon of late onset agranulocytosis should be seen with care and physicians must insist to regular guideline based monitoring of white cell count, even in patients who have been on clozapine for years.

Non-chemotherapy induced agranulocytosis

An adverse reaction observed due to the use of non-chemotherapy drug is agranulocytosis. This occurs as a result of cytotoxic/ immunologic mechanism which lessens the peripheral cell count to less than 0.5 10⁹ cells/dl. [25]. Avoiding the use of drug that causes the disorder can lower the hazardous exposure regarding findings, higher chances are seen in patients with poly pharmacotherapy. Detection of drug-dependent anti-neutrophil antibodies acts as evidence for drug causality [26], on other hand it doesn't have a standard values and it is not exact for drugs that improves this disorder by non-immunologic mechanisms [27]. The treatment that causes non-chemotherapy induced agranulocytosis includes growth factors such as (G-CSF) and (GM-CSF), but occurrence depends on their effectiveness in non-chemotherapy drug-induced agranulocytosis are conflicting [27].

CONCLUSION:

Chemotherapy is rarely seen as a causative agent for this disorder. Genetic manipulation may also include as one of the reason. Agranulocytosis can be recovered in couple of weeks but the mortality and morbidity rate during the initial stage is seems to be high, proper adjuvant treatment with isolation therapy and broad spectrum antibiotics are mandatory for severe neutropenia. Drugs that are treated for this are expected to change as a resistant drug to the patient.

REFERENCES:

1. Uy N, Thiagarajan P, Musher DM. Cephalosporin side chain idiosyncrasies: a case report of ceftriaxone-induced agranulocytosis and review of literature. *Open Forum Infect Dis.* 2015;2(1):ofv007.
2. Yip G, Ekinci E, Lee ST, Jerums G, Grossmann M. Carbimazole-induced agranulocytosis: does antineutrophil cytoplasmic antibody have a role? *Internal Med J.* 2010;40(4):300-303.
3. Robinson J, Richardson M, Hickey J, James A, Pearce SH, Ball SG et al., Patient Knowledge of Antithyroid Drug-Induced Agranulocytosis, *Ur Thyroid J* 2014;3:245-251
4. Patnaik S, Balderia P, Vanchhawng L, Markazi P, Wykretowicz J, Perloff S. Is Levamisole-Induced Vasculitis a Relegated Diagnostic Possibility? A Case Report and Review of Literature. *Am J Case Rep.* 2015;16:658-62.
5. Andrès 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(1):3-8.

6. Ahmad A, Khan MU, Patel I, Maharaj S, Pandey S, Dhingra S. Knowledge, attitude and practice of B.Sc. Pharmacy students about antibiotics in Trinidad and Tobago. *J Res Pharm Pract* 2015;4:37-41.
7. Lhomme F, Ochmann M, Lamy T. Drug-Induced Agranulocytosis. *Rev Prat.* 2015 May;65(5):697-700.
8. Tesfa D, Keisu M, Palmblad J. Idiosyncratic drug-induced agranulocytosis: Possible mechanisms and management. *Am J Hematol.* 2009;84(7):428-434.
9. Andrès E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. *Curr Opin Hematol.* 2008;15(1):15-21.
10. Yang L, Wang K, Chen J, Jegga AG, Luo H, Shi L et al., Exploring Off-Targets and Off-Systems for Adverse Drug Reactions via Chemical-Protein Interactome — Clozapine-Induced Agranulocytosis as a Case Study. *PLoS Comput Biol.* 2011;7(3):e1002016.
11. Opgen-Rhein C, Dettling M. Clozapine-induced agranulocytosis and its genetic determinants. *Pharmacogenomics.* 2008;9(8):1101-1111.
12. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med.* 1993;329:162-167.
13. Senn HJ, Jungi WF, Kunz H, Poldinger W. Clozapine and agranulocytosis. *Lancet.* 1977;1:547.
14. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L. 11- year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet.* 2009; 374:620–627.
15. Gareri P, De Fazio P, De Fazio S, Marigliano N, FerreriIbbadu G, Adverse effects of atypical antipsychotics in the elderly: a review. *Drugs Aging.* 2006; 23:937-956.
16. Oyewumi LK, Al-Semaan Y. Olanzapine: safe during clozapine-induced agranulocytosis. *J ClinPsychopharmacol.* 2000;20(2):279–281.
17. Finkel B, Lerner A, Oyffe I, Rudinski D, Sigal M. Olanzapine treatment in patients with typical and atypical neuroleptic-associated agranulocytosis. *IntClinPsychopharmacol.* 1998;13:133-135.
18. Rajagopal G, Graham JG, Haut FF. Prevention of clozapine-induced granulocytopenia/granulocytosis with granulocyte-colony stimulating factor (G-CSF) in an intellectually disabled patient with schizophrenia. *J Intellect Disabil Res.* 2007;51(Pt 1):82-5.
19. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N Engl J Med* 1993;329:162-7.
20. Pirmohamed M, Park K. Mechanism of clozapine-induced agranulocytosis: Current status of research and implications for drug development. *CNS Drugs* 1997;7(2):139-58.
21. Williams DP, Pirmohamed M, Naisbitt DJ, Uetrecht JP, Park BK. Induction of metabolism-dependent and-independent neutrophil apoptosis by clozapine. *MolPharmacol* 2000;58:207-16.
22. Dunk LR, Annan LJ, Andrews CD. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. *Br J Psychiatry* 2006;188:255-263.
23. Flanagan RJ, Dunk L. Haematological toxicity of drugs used in psychiatry. *Hum Psychopharmacol* 2008;23(S1):27-41.
24. Pessina A, Turlizzi E, Bonomi A, Guizzardi F, Cavicchini L, Croera C, et al. In vitro toxicity of clozapine, olanzapine, and quetiapine on granulocyte-macrophage progenitors (GM-CFU). *Pharmacopsychiatry* 2006;39:20-2.
25. Pisciotta AV. Drug-induced agranulocytosis. Peripheral destruction of polymorphonuclear leukocytes and their marrow precursors. *Blood Rev.* 1990;4:226-37.
26. Stroncek DF. Drug-induced immune neutropenia. *Transfus Med Rev.* 1993;7:268-74.
27. Andersohn F, Konzen C, Garbe E. Agranulocytosis Induced by Nonchemotherapy Drugs. *Ann Intern Med.* 2007;146(9):657-665.

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