

Management of Immune-Mediated Mechanism on Agranulocytosis

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DESCRIPTION

Agranulocytosis is a potentially fatal blood disorder which occurs when the body does not produce enough neutrophils which are a type of white blood cells. White blood cells are immune system components which protect the body from infection by combating germs that cause illness. Agranulocytosis, also known as granulocytopenia, is a severe form of neutropenia. Neutropenia is characterized by lower than normal levels of white blood cells. People with low white blood cell counts are extremely susceptible to infections. They could become ill from germs that would not be harmful otherwise.

Agranulocytosis can be treated with medications by healthcare providers. If left untreated, the condition can lead to serious infections. It can even cause sepsis (a severe infection reaction) and death. Agranulocytosis is classified into two types. It can be inherited (born with it) or acquired. A genetic disorder causes the inherited agranulocytosis. This issue has an impact on how the body produces white blood cells. A rare form of inherited agranulocytosis is immature. Kostmann syndrome or congenital agranulocytosis is other names for it. Infections, fevers, inflammation, bone problems, plague newborns are common with this condition. Certain infections can cause acquired agranulocytosis. It can also be caused by chemical exposure and some prescription medications. Acquired agranulocytosis is frequently caused by cancer treatments and antipsychotic medications. This type of agranulocytosis is also known as drug-induced agranulocytosis.

Immune-mediated mechanism

The immune response could be triggered by the drug directly acting as an antigen, which is unlikely with small molecules but possible or even expected with biological. With small molecules, the drug or one of its metabolites is more likely to act as a hapten and bind covalently to a protein. After uptake by Antigen-Presenting Cells (APCs), cleavage into peptide fragments that occurs intracellular, and surface presentation of these ("foreign") fragments to T-cells *via* the Major Histocompatibility Complex (MHC), the resulting structural change in the affected protein

(antigen formation) can lead to T-cell activation and trigger an immune response.

To function as a hapten, the drug or one of its metabolites must have reactive, usually electrophilic structures capable of reacting covalently with nucleophilic structures of proteins (NH₂, SH, OH groups). -lactams (lactam ring) and 12-hydroxy-nevirapine sulphate, a reactive metabolite of the reverse transcriptase inhibitor nevirapine, are two examples of such compounds with reactive structures. Furthermore, the metabolic epoxidation of aromatic rings, such as that known from the gout agent benzbromarone, is a possibility for the formation of reactive metabolites that react covalently with proteins and can initiate an immune response (in the case of benzbromarone with subsequent liver damage).

Reactive metabolites are most likely produced in the liver by CYP-mediated phase I biotransformation reactions. This also explains why the liver is one of the organs where atypical reactions can occur. The formation of a hapten protein adduct in significant amounts does not necessitate immune activation. This appears to be dependent on the specific product formed, its ability to undergo structural changes, and its reactivity to other molecular structures, as well as the presence of specific molecules interacting with the formed adduct. The latter point, in particular, could explain the low incidence of idiosyncratic drug reactions and their association with specific HLA variants.

Management of agranulocytosis

Agranulocytosis is a serious condition that requires immediate treatment. Any suspected offending medications or agents should be removed once agranulocytosis has been documented, regardless of whether the patient is symptomatic or not. If it is caused by drugs or other offending agents, it usually resolves within one to three weeks of discontinuing the offending agent. Meanwhile, general care such as oral hygiene to prevent mucosal and tooth infection, pain control with anaesthetic gel, and gargles are beneficial. Constipation can be treated with stool softeners. Skin infections and abrasions should be treated as soon as possible.

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Received: 02-Jan-2023, Manuscript No. JHTD-23-21893; **Editor assigned:** 04-Jan-2023, Pre Qc No. JHTD-23-21893 (PQ); **Reviewed:** 18-Jan-2023, Qc No. JHTD-23-21893; **Revised:** 25-Jan-2023, Manuscript No. JHTD-23-21893 (R); **Published:** 02-Feb-2023, DOI: 10.35248/2329-8790.23.11.523.

Citation: Obi A (2023) Management of Immune-Mediated Mechanism on Agranulocytosis. J Hematol Thrombo Dis.11:523

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Hematopoietic growth factors are used to speed up neutrophil production, maturation, migration, and cytotoxicity. Agranulocytosis is treated with filgrastim, a Granulocyte Colony-

Stimulating Factor (G-CSF), sargramostim, a granulocyte-macrophage colony-stimulating factor, and pegfilgrastim (a long-acting filgrastim).