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Agranulocytosis – Causes, Clinical Significance, Management -A Mini Review

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Mini Review

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Introduction

Agranulocytosis is an acute serious and life threatening condition where the absolute neutrophil count (ANC) is less than 100 neutrophils / microliter of blood [1]. It can occur in all age groups. No racial predilection is noted. The typical traid of symptoms in agranulocytosis is

- Fever (which may be the only symptom).
- Sore throat with difficulty in swallowing.
- Inflammatory lesions in mucosae [2].

Agranulocytosis may be inherited or acquired. Inherited or hereditary agranulocytosis also known as Kostmann syndrome is due to a genetic mutation in gene coding for neutrophil elastase (ELA2). Acquired agranulocytosis is more common and usually drug induced (70-95%) [1]. Cytotoxic drugs or high dose immunosuppressants (azathioprine or methotrexate) are commonly implicated. These drugs are used in cancer chemotherapy and act in a dose dependant fashion. Complete blood count is closely monitored for neutropenia which may be the rate limiting step in therapy and warrant a rapid and early intervention.

Agranulocytosis may also occur as a part of idiosyncratic drug reactions. These are less common but can be caused by a wide variety of drugs. Though the exact mechanism causing idiosyncratic reactions is not completely known, it is believed to be immune mediated [3]. The onset is usually 1-6 months after the initiation of therapy and reappears after resumption of medication "rechallenge" due to presence of memory T cells. Agranulocytosis following idiosyncratic drug reactions is HLA associated [4]. The drug may act as an antigen or as a hapten which binds covalently to protein leading to T- cell activation and an immune response. The following is a list of drugs commonly known to cause idiosyncratic reactions.

- Analgesics (diclofenac, ibuprofen, indomethacin, naproxen, phenylbutazone, piroxicam)
- Antidepressants (clomipramine, imipramine, doxepin, maprotiline)
- Anti-convulsants (phenytoin, carbamazepine)
- Anti-infectives (ampillicin, amoxicillin/ clavulanic acid, cefotaxime, ceftriaxone, cephalexin, clarithromycin, gentamycin, piperacillin, trimethoprim/ sulfamethoxazole, norfoxacin, nitrofurantoin, penicillin G).
- Antineoplastic (Flutamide, imatinib, rituximab)
- Antipsychotic (chlorpromazine, clozapine, olanzapine)
- Antirheumatic (sulfasalazine, penicillamine, infliximab)
- Gastrointestinal (cimetidine, omeprazole, ranitidine, metoclopramide)
- Cardiovascular (digoxin,amiodarone, captopril, methyldopa, propranolol, spironolactone)
- Antiplatelet (clopidogrel, ticlodipine)
- Biologicals(infliximab, rituximab, tozillizumab, alemtuzumab)

The most serious complication of agranulocytosis is infection. If ANC is <100 cells / microliter continuously for 3-4 weeks, the rate of infection approaches 100% with sepsis, bacteremia and septic shock the most dreaded outcomes. Old age (over 65 years), presence of comorbid conditions like cardiac failure, renal failure, systemic inflammatory diseases, ANC < $0.1x10^9$/L at the time of diagnosis are considered poor prognostic factors [5].

In case agranulocytosis is diagnosed, prompt treatment should be instituted. Patient needs to be isolated, any suspected offending medication be discontinued. Hematopoietic growth factors (G-CSF) are usually given. In case of proven infection, appropriate antibiotic therapy needs to be instituted. Pharmacovigilance reporting of agranulocytosis occurring as an adverse drug reaction (besides cancer chemotherapeutics) needs to be diligently done. Bone marrow transplant may be required in patients'

not responding to hematopoietic growth factors.

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