Abstract:

Drug induced haematological toxicity consists of a varied group of conditions which can range from asymptomatic to life threatening. We report a patient who presented with a rare manifestation of drug induced haematological toxicity.

Case report:

We present the case of Mrs O, a 32 year old lady from AP, India. She presented with a history of palpitations, weight loss and anxiety lasting for two months, for which she was evaluated elsewhere six months ago. She was diagnosed to have primary hyperthyroidism and initiated on Carbimazole for the same. She reported symptomatic improvement after a period of 10-15 days. However, after one months of initiation of therapy, she started having high grade fever, for which she was symptomatically treated. For the next 4 months she continued to have intermittent fever, which occurred every 5-7 days. Her fever was high grade, and associated with chills.
She also had associated sore throat and oral ulcers with the fever. Whenever she had fever, she received symptomatic therapy for the same, but was never worked up for an underlying etiology.

A month before presenting to us, she started complaining of progressively worsening dyspnea on exertion, which was present on doing accustomed activity. There was no history of cough, sputum or chest pain. For 15-20 days before presentation, she developed bleeding from gums, which occurred spontaneously without any local trauma. She was seen locally, and found to have anemia and thrombocytopenia. She was transfused packed cells for the same, but her Hemoglobin kept dropping. She was ultimately given over 5 packed red cells and referred to us for further management.

On examination, she was found to be pale. There was no icterus, lymphadenopathy, edema or cyanosis. She had sinus tachycardia but was hemodynamically stable. Oral cavity examination revealed a few aphthous ulcers. Further examination revealed bilateral normal vesicular breath sounds. Abdominal examination revealed no organomegaly or tenderness.

Initial laboratory tests revealed pancytopenia (Hb 5.0 g/dl, TC 1300/mm3, Platelets 40000/mm3), with a normocytic normochromic blood picture. She had no abnormalities in the biochemical parameters. The main differentials considered in this case were:

- Disseminated Infection/Bone Marrow Infiltration
- Drug Induced Toxicity
- Autoimmune Disease
- Haematological Malignancy

She was investigated with the above differentials in mind. Her biochemical parameters were normal. Autoimmune markers, including ANA and dsDNA were negative. There was no lymphadenopathy or evidence of tuberculosis on the chest X-ray.

She underwent a bone marrow examination, but no aspirate could be obtained, indicating a dry tap. Examination of the trephine showed scantily cellular marrow with markedly reduced hematopoietic precursors, suggestive of aplastic anemia. There was no evidence of autoimmune disease, disseminated infection or malignancy on bone marrow examination. There was no evidence of excessive marrow fibrosis. She was hence diagnosed to have aplastic anemia, and managed accordingly. In keeping with the temporal profile, the most likely etiology was drug induced aplastic anemia, induced by carbimazole.
Discussion:

Drug Induced Bone Marrow Toxicity: Causes and Epidemiology

Drug induced bone marrow toxicity occurs along a wide spectrum, from mild, predictable leucopenia to more severe cytopenias. Drug induced neutropenia, agranulocytosis and aplastic anemia are serious drug related toxicities which warrant anticipation, early diagnosis and intervention.

A large number of drugs from different classes have been implicated in the pathogenesis, including analgesics, antibiotics, cardiovascular, rheumatologic and psychiatric drugs. (1), (2), (3) Some of the drugs known to cause the same are indicated in Table 1.

Although many drugs have been implicated, a few drugs are more likely to cause such toxicity and warrant awareness of this fact when the drug is initiated.

The frequency of use of many drugs does not correlate with the incidence of these toxicities, and some drugs are remarkably more prone to cause such problems. In a review published in 2007, looking at long term data over a period of 40 years, just 10 drugs accounted for more than 50% of reports of drug induced neutropenia. (4)

These included carbimazole, clozapine, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine. It is important to note that these are non-chemotherapy drugs, and such a reaction indicates idiosyncratic toxicity.

The incidence of mild toxicity is fairly common with these drugs, usually ranging from 1-5 %. (5) Mild asymptomatic leucopenia (TC <4000/ml) is a common reaction with some drugs. It has been found to occur in up to 12% of adults and 25% of children taking Propylthiouracil (PTU), but is usually not severe or persistent enough to warrant stopping therapy. (6) Sulfasalazine has also been found to have mild non-fatal leucopenia in up to 2% of cases, all of which resolve without any long term sequelae. (7)
On the other hand, agranulocytosis occurs at a much lower frequency. This was indicated in a prospective study which followed up over 15000 patients on antithyroid drugs over a period of 12 years. The incidence of agranulocytosis was found to be approximately 0.55% with Propylthiouracil, and 0.35% with methimazole. (8)

Drug induced aplastic anemia is even more uncommon. Only about 40 cases have been reported with antithyroid drugs so far, and all of the reported cases seem to suggest idiosyncratic toxicity. The relative risks of developing aplastic anemia have been reported in various studies that studied long term use of the above list of drugs. The relative risk of developing aplastic anemia has been found to range from 5 to 11 for patients using these drugs. (9) Although the number appears quite large, the absolute risk is low, observing the extremely low incidence of these reactions. Aplastic anemia occurring with anti-thyroid drugs is uncommon, and only about 40 cases have been reported so far in literature.

Mechanisms

The mechanism of development of agranulocytosis and aplastic anemia, though not delineated exactly, are similar. The basic mechanism implicated in most of the drug induced hematopoietic adverse effects is believed to be immune mediated. (10) It can either be a direct insult to the stem cell compartment with the drug or its metabolites, or could be by indirect recruitment of various immunological pathways.

The important fact to remember is that such reactions represent a combination of multiple adverse factors existing at the same time. These include the presence of the drug at the right dose, the level and activity of metabolic pathways, co-existing illnesses, interaction with other drugs, and susceptibility of a person to the toxic effects of a drug. This probably explains the idiosyncratic nature of such reactions and the extremely rare occurrence. The expression of p-glycoprotein (p-gp) on stem cell surface is seen to co-relate with the risk of aplastic anemia, with very low levels being seen in aplastic patients. (11)

The major immunological reactions implicated are as follows:

Production of Novel Proteins: This mechanism is probably how drugs and viruses also can lead to stem cell damage. After exposure, there is expression of new antigens on cell surface, or overproduction of normal antigens. These can act as targets for immunological damage by cytotoxic T cell mediated mechanisms.

Chemically altered Cellular Peptide: A drug can be metabolized intracellularly and the resulting altered protein or drug moiety can be expressed on cell surface. This can stimulate an abnormal immune response against hematopoietic precursors.

Genetically altered Cellular Peptide: Any event causing DNA damage, such as radiation or drug toxicity can lead to expression of an antigen which is normally located, but genetically aberrant.
All these mechanisms lead to T cell mediated immune responses against the stem cell compartment. It is impossible to say who would be at risk for such an event, as the factors affecting metabolism and genetic susceptibility have not been clearly defined for a large number of drugs.

An attempt has been made to delineate such factors, and interestingly, a link has been found between a particular HLA type HLADRB1*08032 and susceptibility to methimazole induced agranulocytosis. (12) Although this is by no means a practical or widely applicable test, it does indicate that the putative mechanism of T cell mediated damage is correct, and therapy should target this abnormal immune activation.

Antibody mediated toxicity has not been found to have a significant role so far. One report exhibited the presence of novel antibodies reacting against hematopoietic precursors, with significant in vitro activity. (13) However, the importance of this mechanism in vivo is not fully understood.

Clinical Features

The appearance of toxicity can occur at any time following therapy, and a previous uneventful exposure does not preclude the appearance of toxicity in the future. (14) The reported time to onset of toxicity is variable, and has ranged from a few days to even years in published literature.

In a systematic review looking at patients from 1988 to 2006, the median duration of treatment before the onset of agranulocytosis ranged from 2 days for dipyrone to 60 days for levamisole and was longer than 1 month for 71% of the drugs studied. Another study looking at anti-epileptic drugs reported a similar variation in duration, ranging from 26 days to 5 years. (2)

The same holds true for antithyroid drugs, where the mean duration to development of agranulocytosis is described as 69 days. The same study also reported mean time to pancytopenia of 41 days. The mean doses of methimazole and PTU used in these patients were 30 mg and 300 mg respectively. (15)

The toxicity of agranulocytosis is usually short lived and reversible. In a retrospective review, the mean time to onset of agranulocytosis was 36 days, with symptoms lasting for a mean of 4.6 days. (16) The same study also reported that the mean period of recovery of cell counts was 7.6 ± 3.4 days, indicating quick reversal of toxicity on stopping the drug. The mean duration of neutropenia has ranged from 8 to 9 days in most reports.

The commonest symptoms reported by patients include fever, followed be sore throat, cough and myalgias. (17)

In another study which reported symptoms, the commonest symptoms again were fever and sore throat, occurring in over 90% of patients. (18)
This is important as the symptoms may mimic minor viral infections, leading to a delay in the diagnosis if a high index of suspicion is not kept. The same study reported Pseudomonas as the commonest organism isolated from blood cultures of these patients, indicating that empiric therapy may be justified in patients who are extremely unwell. However, all patients may not be symptomatic, and in the review cited above, in which 55 (0.4%) patients had agranulocytosis, 43 were asymptomatic and detected only on routine blood count monitoring.

Therapy

There are no recommendations on routine blood count monitoring for anti-thyroid drugs. As indicated in the review above, these complications are very rare, and routine blood count monitoring would not be cost effective. Therefore, the current recommendation is to stop the drug and get blood counts at the earliest signs of fever and sore throat. (19)

Treatment for drug induced agranulocytosis consists primarily of immediately discontinuing the drug and adding a less toxic compound as an alternative.

The usual course is recovery of bone marrow function and normal production of all cell lines within approximately a week. In the review by Andersohn et al, (i) the median duration of neutropenia was found to be 8 days (Inter quartile range, 1-180 days), with a very high proportion (>90%) of patients attaining full recovery.

Many studies have reported the use of colony stimulating factors for shortening the duration of agranulocytosis, and have successfully helped to recover marrow function. As such, G-CSF is recommended for most of these patients to shorten the duration of neutropenia. (20)

As drug induced Aplastic Anemia is extremely rare, no formal guidelines exist as to its management. However, as it has been shown that the mechanism of drug induced aplastic anemia, i.e. T cell mediated cytotoxicity is similar to ‘idiopathic’ aplastic anemia, a parallel can be drawn to treatment. It is quite possible that idiopathic aplastic anemia actually follows a similar pathophysiologic model with yet unknown drugs, chemicals or infections. It is unclear as to the duration one should wait for spontaneous marrow recovery to take place. In the presence of clinical and bone marrow features suggestive of aplastic anemia, it seems prudent to treat as idiopathic aplastic anemia.
Our patient was initiated on therapy with oral cyclosporine, and was discharged after her haemoglobin and platelets stabilized, and was asked to follow up in OPD. However, the patient was lost to follow up.

To summarize, drug induced hematopoietic toxicity is a common adverse event, and can occur on a spectrum from mild to life threatening. Therefore, awareness about its occurrence and the associated drugs would help in early identification and treatment. There are no guidelines for routine monitoring after starting anti thyroid drugs, and patients should be made aware of the common symptoms of agranulocytosis and aplastic anemia and asked to report immediately in case any of those occur. Overall, the prognosis for agranulocytosis seems very good, with data being unclear about the prognosis of drug induced aplastic anemia.

References:


