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Case Report

A challenging case of fenofibrate induced neutropenia

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ABSTRACT

Fenofibrate induced neutropenia is a rare condition. We reported 59-year-old male who developed neutropenia after taking fenofibrate for 20 days. He presented with complaints of fever, upper respiratory tract infection (URTI) symptoms. At presentation his total counts were 800. He was evaluated thoroughly for other causes of neutropenia and was treated with antibiotics, steroids, G-CSF. Once the fenofibrate was stopped, patient counts improved and his symptoms subsided. Hence, it is very important to always keep in mind the possibility of side effects of drugs, however remotely rare they are.

Keywords: Neutropenia, Absolute neutrophil count, Drug-induced, Fenofibrate, Filgrastim

INTRODUCTION

Neutropenia is defined as the reduce count of absolute number of neutrophils in the blood circulation.[1]

Isolated neutropenia without any anemia or thrombocytopenia is seen by physicians and hemotologists in day today practice. It needs to be evaluated properly.[2]

The absolute neutrophil count (ANC) is seen as product of the total leucocyte count and the percentage of neutrophils and band cells seen in the peripheral blood by a differential leucocyte count.[3]

Neutropenia can be divided as mild neutropenia with an ANC of 1000-1500/µl, moderate neutropenia having ANC of 500-1000/µl, or severe neutropenia with an ANC of less than 500/µl. Patients with severe neutropenia are prone for major pyogenic infections and life-threatening infections.[1]

Drug-induced neutropenia was first reported by Kracke in 1931, followed by administration of analgesic (pyramiden) in patients with agranulocytosis. The drug was then eliminated.[3]

Drug-induced neutropenia causes ANC below 500/µl. It has around 2.5%-10% mortality rate. It is more commonly seen in elderly population as they take multiple drugs for their aliments. The common drugs causing severe neutropenia are antithyroid medications, ticlopidine, clozapine, sulfasalazine, trimethoprim-sulfamethoxazole, rituximab and dipyrone. If the causative agent is identifiable, drug induced neutropenia is sometimes reversible at withdrawal of the suspected drug.[1]

Drug-induced agranulocytosis can lead to death if there is a continued exposure to the drug. Any acute severe neutropenia in adult/elderly should be treated as drug-induced until proven otherwise.[4]

Fenofibrate is a fibric acid derivative. It is FDA approved for the treatment of hypertriglyceridemia, primary hypercholesterolemia, or mixed dyslipidemia. It activates peroxisome proliferator-activated receptor alpha (PPAR-alpha), which upregulate lipoprotein lipase, induced high-

density lipoprotein (HDL) synthesis, and decrease liver production of apolipoprotein C. It results in the reduction of plasma triglycerides and very-low-density lipoprotein (VLDL) levels and controlling dyslipidemia condition.[6]

Fenofibrate is well-absorbed after oral administration. It reaches peak plasma concentration reaching within 4 to 8 hours. About 99% of the drug is protein-bound. The dose recommended for the treatment of hyper-glyceridemia is 54 mg to 160 mg daily, primary hypercholesterolemia is 160 mg, mixed dyslipidemia is 160 mg.[6]

The most common side effects of fenofibrate are headaches, dizziness, back pain, joint pain, asthenia, diarrhea, nausea, constipation, dyspepsia, cough, wheezing, nasopharyngitis, and flu-like symptom[6].

It can also lead to certain severe side effects like elevated liver enzymes and creatinine phosphokinase levels (CPK), cholelithiasis, arrhythmia, pulmonary embolism, pancreatitis, agranulocytosis, and myocardial infarction.[6] In such cases either complete stoppage of the drug or dose adjustment needs to be done.

We presented a case of middle-aged man, who was stable and later developed severe neutropenia after starting fenofibrate.

CASE REPORT

A 59-year male, presented with the complaints high grade fever with chills since 4 days. He had difficulty in swallowing and sore throat since 3 days. He had significant voice change and was suffering from severe muscle pain and myalgia.

He is a known case of hypertension, type 2 diabetes mellitus, dyslipidemia with grade-1 fatty liver. His was on metformin 500 mg BD, glimipride 1 mg ½ tablet in the night time, telmisartan 20 mg in the morning, ursodeoxycholic acid 300 mg BD and rosuvastatin 5 mg at night time. Patient was started on rosuvastatin for dyslipidaemia but on follow up his triglyceride levels were 212 in view of which the medication was changed to rosuvastatin and fenofibrate 5/160 mg at night time. At the time of follow up his hemoglobin was 13, platelet was 199×10^3, total count was 6,100. After taking the medication for 20 days he started developing severe myalgia and weakness following which he stopped the drug.

Patient also had an episode of severe neutropenia in 2016 following viral infection. He developed disseminated mucormycosis during the same episode and was medically treated with amphotericin and posaconazole. Repeat PET scan done post treatment showed complete clearance of infection. Bone marrow examination done twice was normal. Following which he was asymptomatic and was fine till the recent hospital visit.

At the time of presentation his complete blood count showed haemoglobin of 12.8, total counts of 800, neutrophils 600, platelet count was 283×10^3. His ESR was 27, serum creatinine level was 1.24, his liver function tests were deranged with total bilirubin of 1.82, SGOT/ SGPT of 27/77, ALP was 88, GGT done was 399. HbA1c was 6.5 suggesting good diabetic control. Ferritin levels done were 348.7, CRP was 136.72. HIV, HCV, HbSAg done were negative.

On examination he was febrile and throat examination was done which showed congestion and redness, he was dehydrated. Initial suspicion of viral fever induced neutropenia was suspected. Infectious disease opinion was taken for fever and neutropenia and was started on broad spectrum antibiotics, oral anti-fungal medication and he was further investigated. Chikungunya and dengue serology, EBV IFA done were negative, procalcitonin done was 0.3. CPK levels were 50 and was done to rule out rhabdomyolysis. RA factor done was borderline positive with 26.8. ANA and ANA profile done were negative. Immunoglobulin levels of IgG were 697, IgM were 56.4, IgA were 220 and were with in normal limits. Flu panel and covid gene x-pert done were negative. CMV PCR, blood culture, urine culture and throat culture done were negative. Serum ACE levels done were 24 and within normal limits.

ENT opinion was taken and he was started on oral gargles. Hemato-oncology opinion was taken and bone marrow aspiration and biopsy were done. He tolerated the procedure well. Peripheral blood smear done showed normocytic normochromic blood picture with neutropenia, reactive lymphocytes were present (Figure 1).

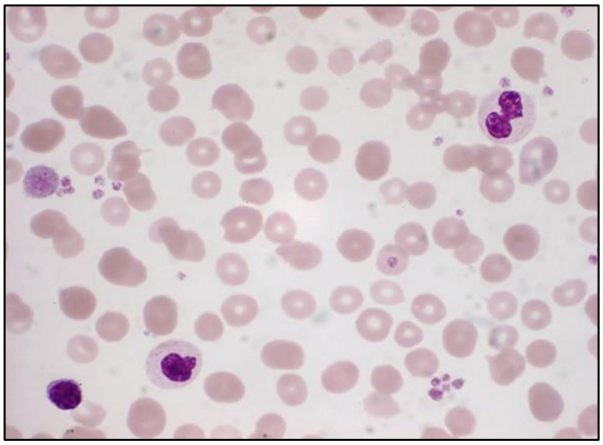

Figure 1: Blood picture of normocytic normochromic blood picture with severe neutropenia.

His chest X-ray done showed bilateral infiltrates (Figure 2) and hence HRCT thorax was done to rule out any invasive infections. HRCT done showed focal eventration of left dome of diaphragm posteriorly with basal atelectasis (Figure 3).

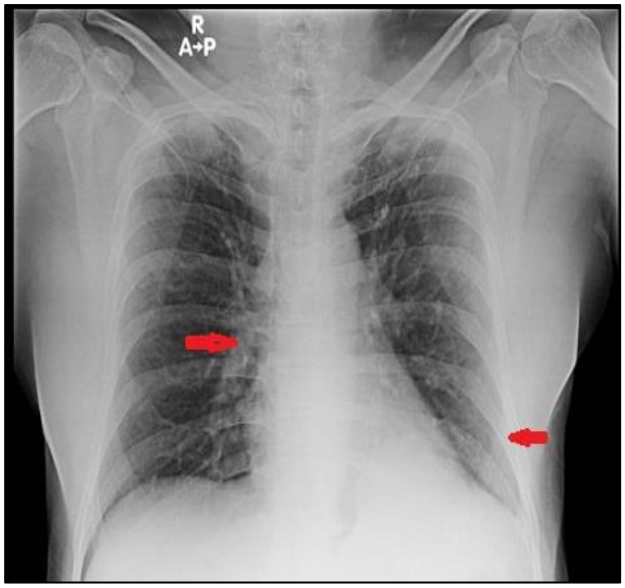

Figure 2: Chest X-ray of bilateral infiltrates.

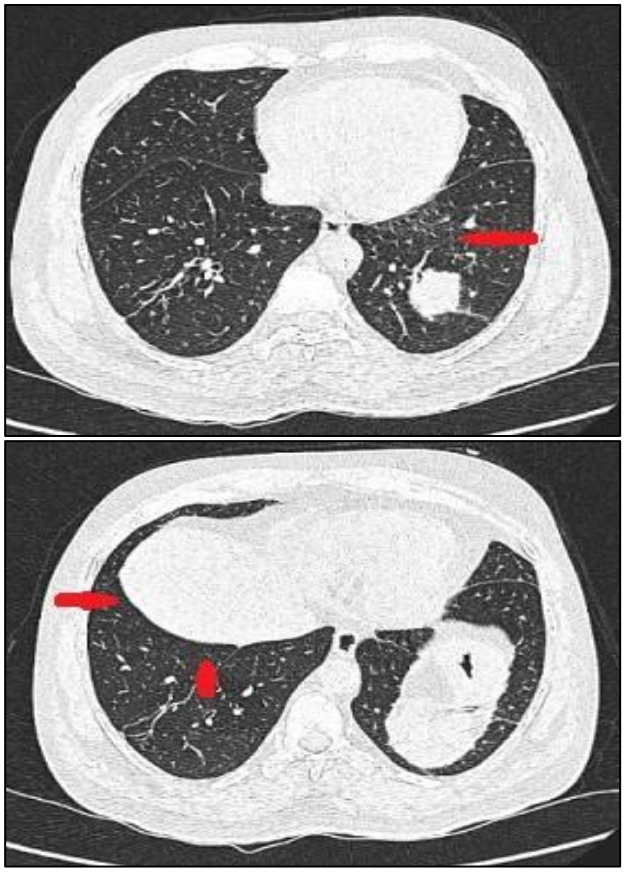

Figure 3: HRCT thorax showed basal atelectasis on right side with eventration of left dome of diaphragm.

Bone marrow aspirate done showed plasma cells of 5%, increase in marrow histiocytes with occasional hemophagocytes. Hence, Secondary hemophagocytic lymphohistiocytosis (HLH) was suspected (Figure 4). He was further evaluated for the same. LDH done was 115, triglycerides were 165, repeat serum ferritin was 597 and he was started on intravenous (IV) hydrocortisone 100 mg BD.

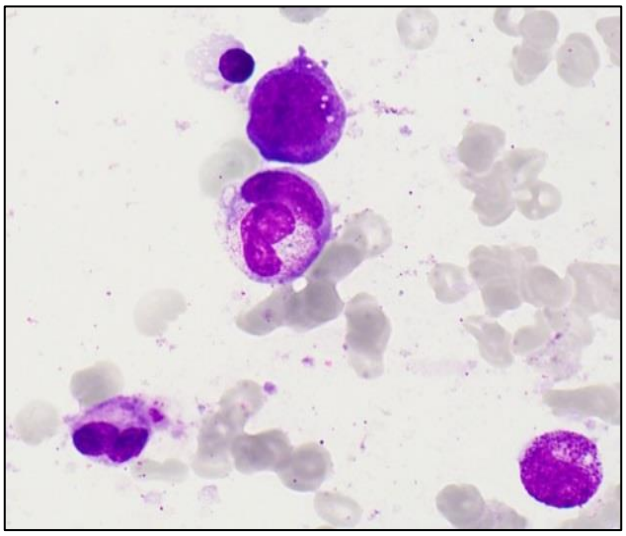

Figure 4: Bone marrow aspirate suggestive of hemophagocytic lymph histiocytosis (HLH).

His repeat CRP renal profile and complete blood counts showed persistent neutropenia and low total counts, reduced haemoglobin levels of 10.1 with elevated creatinine of 1.6 and elevated CRP of 343. He continued to have high grade fever with profuse sweating and weakness. At this point the patient developed bicytopenia in complete blood counts. After discussing the case with hemato oncologist he was started on filgrastim injection subcutaneously 300 µg OD dose. Hydrocortisone was stopped and was changed to dexamethasone 8 mg infusion BD.

Bone marrow biopsy report done showed mildly hypocellular marrow with erythroid predominance, a mild increase in marrow macrophages were seen in interstitium. Repeat peripheral smear showed normocytic hypochromic anemia with leucocytosis. Differential counts showed relative increase in lymphocytes and monocytes.

In view of sterile culture his antibiotics were gradually tapered and were stopped. HLH was ruled out in view of normal serum LDH, borderline triglycerides, and reduced myeloid series with normal erythroblasts in bone marrow biopsy report.

Prolonged neutropenia secondary to drug induced? Fenofibrate was suspected. Hence, GCSF and IV steroids were continued.

Patient fever spikes gradually subsided and his complete blood counts and renal profile also showed improvement with increase in total counts and increase in ANC and serum creatinine levels were normalized. His sugars were closely monitored and were well controlled. After 1 week

of intravenous dexamethasone infusion, he was gradually shifted to oral steroids which were later tapered.

Post treatment his complete blood counts showed total counts of 56.7, with ANC of 88.1, platelets were 430×10^3, haemoglobin of 10.9. Table 1 shows his total count and N/L ratio and ANC during the hospital stay. Repeat peripheral blood smear showed normocytic normochromic blood picture with neutrophilic leucocytosis shift to left with good number of metamyelocytes and myelocytes. Filgrastim was stopped and he was monitored. Patient was in stable condition and was afebrile. He was discharged with oral steroid medications on tapering doses. At follow up patient was doing well and was afebrile. His complete blood count was normal with total count of 8890, N/L-65.2/28.6, hemoglobin-12.3 and platelets of 211×10^3 after 3 weeks of stopping finofibrate.

Table 1: Patient's total count, N/L ratio and ANC during his stay in hospital.

Date	TLC	N/l ratio	ANC
4/5/2022	800	0.6/95.5	0
6/5/2022	600	0.7/95.5	0
8/5/2022	600	0.4/96.6	0
9/5/2022	800	1.7/96.1	0
10/5/2022	600	1.3/81.1	0
11/5/2022	900	2.3/63.9	0
12/5/2022	1,700	10.8/56.9	0.2
13/5/2022	2,600	23.5/38.5	0.6
16/5/2022	56,700	88.1/5.1	49.9
18/5/2022	49,600	94/4.1	46.6
26/5/2022	9800	51.8/45.7	-
31/5/2022	8890	65.2/28.6	-

Since, patient showed improvement in counts after stopping fenofibrate, and all other work up was negative, we associated the neutropenia secondary to drug. Even though it is rare, it has been documented that fenofibrate can cause severe neutropenia and anemia. Hence, it was a very challenging and peculiar case to treat. The cases of severe neutropenia need to be evaluated thoroughly and complete drug history is very vital for management.

DISCUSSION

Acquired neutropenias are common than congenital neutropenias. They are most commonly seen after infections or after exposures to drugs. As in the case discussed above, our patient had normal complete blood count prior to starting fenofibrate. It can also be caused secondary to autoimmune condition or due to nutritional deficiency.

Acquired neutropenias can be caused by hypersplenism or as a result of a hematological malignancy. In most cases of neutropenia cause cannot be found and hence treated as chronic idiopathic neutropenia.[2]

Patients having neutropenia are prone for repeated infections. It commonly involves the oral cavity and mucus membranes, presenting as oral ulcers, pharyngitis, and periodontitis. It also involves skin causing rashes, ulcerations, abscesses, and poor wound healing. These patients also prone for perirectal and genital infections. They can also present with systemic infections involving lungs, gastrointestinal tract, and blood stream can lead to death in patients with persistent severe neutropenia.[3]

Staphylococcus aureus, *Staphylococcus epidermia*, *Streptococci*, *Enterococci*, *Pseudomonas aeruginosa*, other gram-negative bacilli are the most common bacterial infections seen in patients with severe neutropenia.[1]

Now looking at the fungal infections in neutropenic patients Candida albicans; and other candida species such as *C. tropicalis*, *C. glabrata* and *C. parapsilosis* causes common oral and gastrointestinal tract infections in these cases. Infections with *C. krusei* were seen in medical centres where fluconazole was used for prophylaxis for fungal infections. *A. fumigatus* or *A. flavus* causes aspergillosis in neutropenic patients. Even though, aspergillosis causes pneumonia it can also lead to other serious infections like invasive rhinosinusitis, cerebral infection and disseminated infection. Other rare fungi that can lead to systemic infections in neutropenic patients are *fusarium*, *cryptococcus*, *trichosporon*, *rhizopus*, and *rhizomucor*.[3] Infection with any virus can lead to neutropenia in children., but it is seen mostly after infection with varicella, measles, rubella, influenza, hepatitis, Epstein-Barr virus and HIV infection.[2]

As per our case above the patient presented with severe flu like symptoms with pharyngitis and high-grade fever with led us to suspect infective causes of neutropenia initially.

Drug-induced neutropenia

The pathogenesis of drug-induced neutropenia is not properly understood, though several theories have been proposed. In some cases, neutropenia was seen after prolonged exposure to drugs, resulting in decreased myeloid production leading to a hypoplastic bone marrow.

In few other cases it was seen after repeated but intermittent exposure to offending agents. It was theorized that it could have been due to an immune mechanism or secondary to antineutrophil Abs. According to Bhatt et al various mechanism of action of drug induced neutropenia has been put forth.[3]

Immune mediated neutropenia

Neutropenia occurring is rapid in onset, with in few hours to 1-2 days. It was mostly seen in patients who had prior exposure to the drug.[3]

Hapten: Drugs like aminopyrine, penicillin, and gold compounds act as haptens. They lead to antibody formation against the neutrophils leading to the destruction.[3]

Apoptosis: Neutrophils have a life span in the circulation of 8 to 20 hours. Drugs like clozapine accelerates the process of apoptosis.[3] After taking Clozapine for 3 months around 1% of patients developed neutropenia.[1] In chronic clozapine therapy, the mechanism that was proposed was the drug lead to haptenation of polymorphonuclear cells leading to depletion of ATP and glutathione is also depleted, leading to apoptosis.[3]

Immune complexes: Circulating immune complexes may be formed, which bind to neutrophils and cause their destruction.[3]

Complement mediated mechanism: Akamizu et al reported a patient with Grave's disease who was on propylthiouracil therapy had developed neutropenia and anti-neutrophil cytoplasmic antibodies (ANCA). ANCA disappeared after the withdrawal of the drug.[9]

Dose-dependent inhibition of granulopoiesis: At high concentration, few drugs lead to inhibition of colony forming units of granulocytes and macrophages in all bone marrow samples.[3] Beta-lactam antibiotics, carbamazepine and valproic acid are examples of drugs.

Direct toxicity for myeloid precursors: Cytotoxicity of ticlopidine for pluripotent or bipotent hemopoietic progenitor stem cells was studied by Symeonidis et al.[10] It was noted that it was a reversible cause.

Similar to our case, a rare case was reported by Kacirova et al a middle-aged man was treated with fenofibrate developed anemia and neutropenia. After stopping the drug for 3 weeks his haematological parameters were normalized. The exact mechanism by which fenofibrate causes neutropenia and anemia are not understood. But one hypothesis of drug allergic reaction was put forward as the probable cause.[5]

Management

G-CSF introduction in the late 1980s lead to an effective management of neutropenia.[1] Recombinant human granulocyte colony stimulating factor (rG-CSF). G-CSF is the major cytokine that stimulates the growth and development of neutrophils in the bone marrow. A recombinant form of G-CSF (filgrastim; r-metHuG-CSF) is commercially available.

Filgrastim has the same pharmacological effects as endogenous human granulocyte colony stimulating factor G-CSF. It leads to the activation, proliferation, and differentiation of neutrophil progenitor cells and improves the function of mature neutrophils. It causes granulopoiesis without reducing the half-life of neutrophils.[3] G-CSF is given for the patients with recurrent or severe infections or symptomatic mucosal erosions or skin infections.[2]

rG-CSF treatment along with IV antibiotics treatment led to decrease in the number of hospitals stay to decrease the number of days stay in hospital by 50% in neutropenic cases.[3]

Hence it is essential to start the treatment to reduce the mental and financial strain on the family due to prolonged hospitalization. Peg filgrastim, also showed sustained colony-stimulating factor effect. It is used to prevent chemotherapy-induced neutropenia (CIN) in patients with high-risk breast cancer and in patients with lung cancer and non-Hodgkin's lymphoma. It was administered (100 µg/kg) once per chemotherapy cycle.it showed similar results like that of daily filgrastim (5 µg/kg) dose. Peg filgrastim was also found safer.[3]

Penicillamine therapy is used in treatment of neutropenia associated with gold or arsenic exposure.[3] The incidence of leukemia in patients with Severe congenital neutropenia (SCN) is around 10%-20%. Patients with and without ELANE mutations were similarly affected after 15 years of treatment.

At least quarterly CBCs and annual bone marrow aspirations with cytogenetics should be performed in these cases. The requirement for doses of G-CSF exceeding 8 µg/kg is an indicator of risk.[1] Plasmapheresis, splenectomy and cytotoxic drugs are used as other modalities of treatment in neutropenic cases that are not responding to conventional therapy.[7]

CONCLUSION

Elderly age group are more prone for drug-induced neutropenia and leads to long term debilitating effects. Hence, when a patient presents with neutropenia a proper history and examination and complete work up needs to be done. Complete list of medications and the adverse effects should be kept in mind. Even most commonly used medications can cause serious side effects, if investigated properly repeat episodes of neutropenia and repeat hospitalizations and financial burden on family can be prevented, as it is the most common preventable cause of neutropenia. Fenofibrate is most commonly used dyslipidemic drugs in both IP and OPD patients. Although fenofibrate-induced anemia and neutropenia is rare, patients receiving fenofibrate should be monitored for adverse drug reaction. For many years, neutropenic patients were treated with antibiotics during febrile episodes. The development of the hematopoietic growth factors, like G-CSF, has made tackling neutropenia more efficient and effective.

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