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Case Report

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A Complication of Statin Therapy: Atorvastatin-Induced Agranulocytosis

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Abstract

We present a 70-year-old male with progressive generalized weakness and bilateral lower extremity pain found to have severe neutropenia, elevated serum creatine kinase, and elevated transaminases. The patient had recently started high dose atorvastatin for coronary artery disease and hyperlipidemia. Other potential causes of acute severe neutropenia were ruled out. All home medications were continued during the hospitalization except for atorvastatin. Within three days of atorvastatin discontinuation, the patient's symptoms and laboratory abnormalities improved significantly. This case highlights the importance of considering statin-induced neutropenia in the differential diagnosis of acute neutropenia.

Keywords: Atorvastatin side effects; Isolated neutropenia; Drug induced agranulocytosis

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Introduction

Drug-induced acute severe neutropenia is a rare and serious adverse event, with an annual incidence between 2.4-15.4 cases per million over the past twenty years, despite the availability of new causative medications [1]. Neutropenia is defined as an Absolute Neutrophil Count (ANC) less than 1500 cell/μL. Severe neutropenia, or agranulocytosis, is defined as an ANC below 500 cells/μL. The majority of cases of severe acute neutropenia in adults, without coexistent anemia and thrombocytopenia, are due to drug- or toxin-induced agranulocytosis [2]. Drug-induced neutropenia usually occurs within 3 months of starting the offending medication [3]. Because the duration and severity of neutropenia directly increase the risk of life-threatening infection, early recognition and identification of the etiology is crucial for management.

Case Report

A 70-year-old Filipino male with stage 3 chronic kidney disease, ischemic cardiomyopathy, essential hypertension, and gout presented with a one-week history of progressive fatigue and bilateral calf pain. Less than three months prior to this presentation, he was admitted to the hospital for diverticulitis. That hospitalization was complicated by a Non-ST-Elevation Myocardial Infarction (NSTEMI) and acute decompensated heart failure. A drug-eluting stent was successfully placed and he was discharged with aspirin, clopidogrel, high dose atorvastatin (80 mg), felodipine, furosemide, and metoprolol. He had not been taking any chronic medications prior to that hospital stay.

After discharge, he reported adherence with his medications and was in good health until one week prior to this admission, when he began experiencing fatigue, loss of appetite, and bilateral calf pain described as cramping, intermittent, 5/10 in severity, non-radiating, aggravated by walking, and alleviated by rest. He denied fevers, chills, night sweats, upper respiratory symptoms, gastrointestinal symptoms, headache, chest pain, focal weakness, and skin rashes.

In the emergency department, he was hemodynamically stable though he endorsed mild shortness of breath. His exam was only remarkable for tenderness to palpation on bilateral calves. Initial laboratory tests **(table 1)** revealed leukopenia with agranulocytosis, baseline mild anemia and thrombocyte-

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penia. The peripheral blood smear showed severe leukopenia without other abnormalities to suggest a specific etiology. Liver tests revealed elevated transaminases. The chest x-ray and urinalysis were unremarkable. During the hospitalization, the etiology of the acute neutropenia was investigated broadly, including testing of serum Anti-Nuclear Antibody (ANA), Anti-Neutrophil Cytoplasmic Antibody (ANCA), rheumatoid factor, HIV, hepatitis A IgM, hepatitis B surface antigen, hepatitis C antibody, Ebstein-Barr Virus (EBV) IgM, Cytomegalovirus (CMV) IgM and IgG, parvovirus IgM and IgG, vitamin B12, TSH, folic acid, and blood cultures. All serum markers and blood tests were unremarkable, except for an elevated ANA (1:80) with a diffuse pattern, equivocal CMV IgM level, and positive CMV IgG. Given the bilateral calf pain, elevated creatine kinase, and elevated serum transaminases, atorvastatin was discontinued, while his other home medications, including aspirin, felodipine, clopidogrel, and metoprolol, were continued.

Table 1: Laboratory data.

CBC	Day 1	Discharge day	2 months later	Normal range
Hemoglobin	11.2*	9.0*	11.5*	13.7-17.5 g/dL
Hematocrit	33.8*	27.1*	35.5*	40.1-51.0 %
WBC	0.84*	3.12*	16.56*	3.80-10.80 x10(3)/uL
Neutrophil	0.00*	38.0*	38.9	34.0-72.0 %
Absolute neutrophil count	0*	1200*	6441	> 1500 cell/microL
Lymphocyte	66.7*	26	27.1	12.0-44.0 %
Monocyte	15.5*	26.0*	4	0.0-12.0 %
Eosinophil	9.5*	0	28.9*	0.0-7.0 %
Basophil	8.3*	0	0.8	0.0-2.0 %
Band form	0	0	0	0.0-1.0 %
Platelet	151	144	141	151-424 x103/uL
MCV	86.2	82.6	87	79.4-98.4 fL
MCHC	33.1	33.2	32.4	32.0-36.0 g/dL
RDW	15.7	15.3	15.7	11.6-14.4 %
Chemistry	Day 1	Discharge day	2 months later	Normal range
Glucose	141	111	123	70-99 mg/dL
BUN	78*	72*	66*	6-23 mg/dL
Creatinine	4.6*	4.7*	5.2*	0.6-1.4 mg/dL
Sodium	135	133	140	133-145 mEq/L
Potassium	4.3	3.8	4.1	3.3-5.1 mEq/L
Chloride	95	92	102	95-108 mEq/L
HCO3	16	24	17	21-30 mEq/L
ALP	533*	318*	111	35-129 IU/L
AST	232*	164*	20	0-40 IU/L
ALT	202*	157*	12	0-41 IU/L
Total bilirubin	1.5*	0.8	0.7	0-1.2 mg/dL
Direct bilirubin	0.6	-	0.2	0-0.3 mg/dL
Indirect bilirubin	0.9*	-	0.5	0-1.0 mg/dL
CK	3698*	3525*	62	39-308 IU/L
LDH	774*	-	-	135-250 IU/L
Haptoglobin	91	-	-	30-200 mg/dL
Folic acid	9.2	-	-	>3.1 ng/mL
TSH	1.31	-	-	0.27-4.20 uIU/mL
Vitamin B12	1124	-	-	211-946 pg/mL
Serum markers	Day 1		2 months later	Normal range
ANA	80 with diffuse pattern*		-	0
Rheumatoid factor	< 10		-	<10
EBV IgM	Negative		-	Negative
Parvovirus IgM	Negative		-	Negative
HIV ½ antibody	Negative		-	Negative
CMV IgM	Equivocal		-	Negative
CMV IgG	Positive		-	Negative
ANCA	Negative		-	Negative
Hepatitis A IgM	Negative		-	Negative
Hepatitis B surface antibody	Negative		-	Negative
Hepatitis B surface antigen	Negative		-	Negative
Hepatitis C antibody	Negative		-	Negative

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Three days after the discontinuation of atorvastatin, the patient's ANC increased from 0 to 1185 cell/μL and his bilateral calf pain resolved. On discharge, he was instructed not to take the atorvastatin, but to continue all of his other previous medications. Two months later, he was admitted with acute decompensated heart failure. His liver tests, creatine kinase, and white blood cell counts were normal at that time.

Discussion

The patient developed acute agranulocytosis within three months of starting new medications for his heart disease. During his hospitalization, his medications were continued except for atorvastatin, which was discontinued due to his elevated transaminases and rhabdomyolysis. He did not receive antibiotics or other interventions beyond intravenous hydration. Further investigations of the cause of his acute agranulocytosis were unremarkable, including HIV antibody, Parvovirus IgM, EBV IgM, vitamin B12 level, TSH, ANCA, blood culture, urinalysis, and chest x-ray.

His minimally elevated ANA (1:80 with a diffuse pattern) was nonspecific and not associated with clinical features of drug-induced lupus, such as fever, skin rash, joint pain, or pleuritis [4]. An elevated ANA with a diffuse pattern could be due to a drug reaction or represent a benign false positive finding [5].

Serologic testing showed equivocal CMV IgM and positive CMV IgG, suggesting waning immunity after remote primary CMV exposure [6]. Symptomatic CMV infection typically occurs in immunocompromised hosts, especially those with HIV infection, organ transplants, or malignancy receiving chemotherapy [7]. The clinical manifestations are variable, but the most common presentations are a mononucleosis-like illness, fever of unknown origin, hepatitis, retinitis, colitis, pneumonitis, and general myelosuppression. Furthermore, severe symptomatic CMV infection should be treated with antivirals such as gancyclovir. In our case, the lack of risk factors and systemic symptoms, along with the rapid recovery without antiviral treatment, make CMV infection an unlikely cause of the agranulocytosis [7].

Three days after discontinuation of atorvastatin, the patient's ANC rose above 1000 cell/μL and his symptoms resolved. Two months later, while off statin therapy, his white blood cell count, creatine kinase, and liver tests remained normal.

Idiosyncratic drug-induced agranulocytosis should be suspected in patients with acute agranulocytosis without evidence of worsening thrombocytopenia and anemia. The most common causative medications are antibiotics (beta-lactams and cotrimoxazole), antiplatelet agents (ticlopidine), antithyroid drugs, sulfasalazine, neuroleptics (clozapine), antiepileptic agents (carbamazepine), nonsteroidal anti-inflammatory agents, and dipyrone. Drug-induced agranulocytosis frequently appears within 3 months of starting the offending medication and the pathophysiology is thought to be immune-mediated destruction of circulating neutrophils [8]. A diagnosis of drug-induced agranulocytosis is supported by clinical improvement and upward trend of neutrophils following discontinuation of the offending medication. Bone marrow biopsy is generally indicated for cases with unexplained or persistent pancytopenia suspected medication discontinuation.

While atorvastatin is frequently prescribed for cardiovascular risk reduction and generally well tolerated, adverse effects can occur. Commonly reported adverse reactions include myopathy and liver injury, but there is limited literature describing hematologic toxicity. This case adds to the literature suggesting atorvastatin may rarely cause severe neutropenia.

Conclusion

Early recognition of the underlying cause of acute severe neutropenia is essential because the risk of serious infection is related to the duration and severity of the neutropenia. Drug-induced agranulocytosis commonly occurs within three months of the initiation of the offending medication and should be suspected when severe neutropenia presents without concomitant thrombocytopenia or anemia [3] Once agranulocytosis occurs, the suspected medication should be discontinued permanently, as re-challenge may increase the risk of recurrent neutropenia through an underlying immune mediated mechanism [9]. This case highlights the importance of considering even previously unreported adverse drug events when the clinical chronology suggests an association. Timely recognition and removal of the culprit medication can lead to improvement and prevent related complications.

Learning Points

- Drug induced agranulocytosis should be considered in patients presenting with isolated severe neutropenia even if the drug is not commonly associated with hematologic toxicity;
- Atorvastatin is widely prescribed and generally well tolerated, but may have rare adverse effects such as agranulocytosis and;
- Timely discontinuation of the suspected offending medication is important for hematologic recovery and prevention of complications.

Disclosure

A preliminary version of this case was presented as an abstract at the Endocrine Society Annual Meeting in 2017 and was published in abstract form in Endocrine Reviews.

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Conflict of Interest

The authors disclose no conflict of interest.

Patient Consent

We obtained informed consent from the patient to secure permission to publish his clinical history.

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