

Simvastatin-induced pleuro-pericardial effusion and megaloblastic anemia

Abstract

Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver. Statins are considered for all patients with cardiovascular diseases such as coronary heart disease, peripheral vascular disease, non-haemorrhagic stroke, and transient ischemic attacks. Pleural and pericardial effusions may be caused by infectious diseases, malignancies and autoimmune disorders. However, unexplained effusions should raise the possibility of drugs as being the cause. Drug-induced anemia may be in the form of auto-immune or oxidative hemolysis, aplastic anemia, sideroblastic anemia or megaloblastic anemia. I report a case of lymphocytic pleural effusion, pericardial effusion and megaloblastic anemia in a patient known to have ischemic stroke, diabetes mellitus and hypertension. In the view of unyielding clinical and laboratory evaluation, a drug-induced reaction was suspected. Because of the recent addition of Simvastatin to the patient's regimen, the improvement of the patient's condition after discontinuation of Simvastatin and recurrence of symptoms following its re-administration, a conclusion was made that Simvastatin may be the cause of the patient's clinical picture and should be further considered as a cause of unexplained pleural and pericardial effusions, and megaloblastic anemia.

Keywords: statins, simvastatin, drug-induced pleural effusion, drug-induced pericardial effusion, drug-induced megaloblastic anemia

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Introduction

Statins, the usual prescribed lipid-lowering drugs, inhibit the HMG CoA reductase and increase the expression of low-density lipoprotein (LDL) receptors in the liver, allowing a reduction in the LDL serum levels and provide a significant decrease in cardiovascular mortality.^{1,2} The commonest side-effects are muscle pain, myopathy, rhabdomyolysis, and elevations of hepatic enzyme.³ Lupus-like syndromes, hypersensitivity pneumonitis and Pseudopolymyositis, have been, also, reported.⁴ Moreover, Lovastatin was reported to cause hemolytic anemia, and Pravastatin sodium has been reported to cause bilateral lymphocytic pleural effusion without any lung or extra-thoracic abnormalities.^{5,6}

Drug-induced hematologic disorders can affect any cell line, including white blood cells (WBCs), red blood cells (RBCs), and platelets. Drugs can affect RBCs by causing a number of different anemias, including drug-induced immune or oxidative hemolytic anemia, sideroblastic anemia, aplastic anemia, red cell aplasia, or drug-induced megaloblastic anemia.^{7,8}

Drug-induced pleural reactions may occur in the absence of parenchymal lung disease and usually manifest as pleural effusions. However, pleural thickening with or without pleural effusion, pleuritic chest pain, and in even fewer cases, pneumothorax or hemothorax, may, also, occur.^{9,10} The pathological mechanisms explaining these reactions are not clear, but hypersensitivity reactions, oxidative stress of mesothelial cells, dose-dependent toxic effect, fluid retention and induction of chemical inflammation have all been proposed.¹⁰ Generally, Drug induced Lupus pleuritis is the most common cause of drug induced pleural effusion and is associated with high ESR and serum ANA titers. Although histone antibodies are suggestive of the condition, with 50-80% occurrence, they are not specific.¹¹

Case report

A 61 year old female patient with history of ischemic stroke, type 2 diabetes mellitus and hypertension, was admitted with pleuritic chest pain and progressive dyspnea for 4 weeks. She is non-smoker, and denies symptoms of cough, fever, myalgia, arthralgia, skin rashes, anorexia and weight loss. She had no history of allergy or exposure to agents that may harm the respiratory system. Her own medications, over the last 10 years, were Metformin (850mg TD), Glibenclamide (5mg TD), Amlodipine (5mg OD), Enalapril (10mg TD) and Aspirin (100mg OD). Simvastatin (20mg OD) was added to her regimen, 3 months prior to her presenting symptoms, after she suffered an ischemic stroke.

Clinical examination was significant only for pallor, and decreased air entry bilaterally consistent with bilateral pleural effusion on chest X-ray. Further evaluation revealed anemia (PCV 25%, HGB 8.2, MCV 106), normal WBCs and platelets counts without evidence of eosinophilia. Erythrocyte sedimentation rate was elevated (65 ml/1st hour). Chest CT scan was reported with moderate bilateral pleural effusion and pericardial effusion with normal lungs fields and no evidence of pulmonary embolism. 2D-Echocardiography revealed pericardial effusion of 2.3 cm posteriorly and 1.6 cm anteriorly, with no signs of ventricular compression, and 65% ejection fraction. Her blood film was significant for megaloblastic RBCs, few hypersegmented neutrophils and normal platelets.

Therapeutic and diagnostic pleurocentesis was done. Exsudative effusion was evident with LDH 190 IU (0.9 ratio) and total protein 3.9 g (0.56 ratio). Cellular and differential count revealed lymphocytes 65%, neutrophils 33% and eosinophils 2%. There were no malignant cells on cytological study. PCR for mycobacterium tuberculosis DNA was negative.

Erythrocytic hyperplasia, with other megaloblastic changes, was evident on bone marrow biopsy and aspirate. Serum folate and B12 levels, Thyroid function, Creatine kinase, Kidney function and liver function, were all within normal ranges. Electrocardiography was normal with no changes suggestive of Pericarditis. Rheumatoid factor, ANA and anti-dsDNA, and c and pANCA were negative. ACE level was 23 microgram/l.

In the view of her indeterminate clinical and laboratory findings, drug induced pathology was suspected. Because Simvastatin was the most recent drug used in her regimen, it was discontinued. As the patient dyspnea was dramatically improved following pleurocentesis, and chest pain was improved following administration of Paracetamol PRN; she was discharged home, with untouched pericardial effusion and without correction of anemia, and given appointment for follow up. 3 weeks later, the patient had no chest pain, even without pain killers, and had no dyspnea. Her PCV was 29% and HGB was 9.7 g/dl. There were only obliterated costophrenic angles on chest X-ray with evident improvement of Pericardial effusion (1.9 cm posteriorly, 0.8 cm anteriorly). On next appointment, 1 month later; pleural effusion had disappeared, PCV was 33% and pericardial effusion was 0.7 Cm posteriorly. 3 months later, the patient chest X-ray, complete blood count and 2-D echocardiography were all normal and the patient was free of symptoms.

A re-challenge with Simvastatin, for 3 weeks, had reproduce the symptoms of pleuritic chest pain and dyspnea and the patient developed pleural effusion, the drug was discontinued with dramatic improvement of symptoms over the next 4 weeks.

Discussion

Although Drug induced pleural disease is generally underappreciated, its possibility should be emphasized in a patient with a pleural effusion that cannot be explained after the initial work-up for common etiologies.¹¹ The usual presenting symptom in patients with drug-induced pleural disease is dyspnea, which may due to a rapidly increasing pleural effusion or fibrosis, or may be due to an underlying parenchymal lung involvement occurring in association with pleural disease.¹⁰ The onset of Symptoms may be acute, soon after the exposure to a new drug, or may occur years later. However, a time gap of weeks to months is the usual.¹¹ A thorough and meticulous review of drug history, temporal relationship between exposure to a drug and symptoms occurrence, Disappearance of symptoms after discontinuation of a drug and reappearance after drug re-use and evidence of pleural fluid eosinophilia should raise the possibility of a drug-induced reaction.^{9,11} Treatment of drug-induced pleural disease is generally based on Pleural fluid drainage to relieve dyspnea and on discontinuation of the offending drug, which is usually sufficient. Sometimes, when a hypersensitivity reaction is suspected or to reduce pleural inflammation, corticosteroids are prescribed. However, there are no sufficient data to prove corticosteroid efficiency.¹¹

Megaloblastic anemia, a condition that can be congenital or acquired, is associated with a hypercellular bone marrow with large, abnormal hematopoietic progenitor cells (megaloblasts). Pancytopenia may be present. Megaloblastic anemias are generally related to vitamin B12 or folic acid deficiencies resulting from malnutrition or defective absorption, however, megaloblastic anemias can, also, be drug-induced.⁸ Antimetabolites, alkylating agents and some antinucleosides used against HIV; which act by interfering with DNA synthesis, can all induce megaloblastic anemia.¹² Moreover, some

drugs that inhibit dihydrofolate reductase, such as trimethoprim and pyrimethamine, have been associated with megaloblastic anemia primarily in patients at risk for folic acid deficiency. Sulfasalazine and anticonvulsants such as phenytoin interfere with absorption of folate and may induce megaloblastic anemia.⁸

Simvastatin/Ezetimibe was reported to cause lymphocytic pleural effusion with high antinuclear antibodies (ANA) and without clinical signs of a rheumatologic syndrome.¹³ Also, treatment with Simvastatin had been reported to cause pleural effusions after 6 months to 13 yrs of therapy initiation,^{14,15} but to the best of the present authors' knowledge, this is the first case of pericardial effusion and megaloblastic anemia, with normal B12 and folate levels, expected to be caused by Simvastatin. Furthermore, in the patient reported here, the absence of interstitial lung fibrosis, peripheral or pleural fluid eosinophilia, high ANA and abnormal liver function or weight loss, which were present in previously reported Simvastatin-induced pleural effusions, suggests that different mechanisms could be responsible for pleural diseases induced by simvastatin.

Conclusion

Attributing a clinical condition to specific drug intake, after exclusion of other potential causes, may prove a complicated scenario. Statins intake should be considered as a cause of unexplained lymphocytic pleural effusion, pericardial effusion and megaloblastic anemia. In the view of normal serum folate and B12 levels, the mechanism of Simvastatin-induced megaloblastic anemia needs further evaluation.

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None.

Conflicts of interest

The author declares there is no conflict of interest.

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