中文題目：Amiodarone 引起之肝與肺傷害
英文題目：Amiodarone induced hepatic and pulmonary injury - a case report
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Introduction: Amiodarone is one of the most commonly prescribed antiarrhythmic agents. However, amiodarone is associated with many adverse effects. The common adverse effects include thyroid dysfunction, hepatic toxicity, and pulmonary toxicity. Many studies and case reports have depicted these side effects. However, few articles have reported simultaneous hepatic and pulmonary injury. In this report, we presented a 68-year-old female with both amiodarone related hepatic and pulmonary injury.

Case presentation: A 68-year-old female had a past medical history of rheumatic heart disease in her youth. The rheumatic heart disease complicated with severe MR. She received mitral valvuloplasty in her 30s, but mitral regurgitation and tricuspid regurgitation recurred after the surgery. She also had longstanding persistent atrial fibrillation noticed for more than fifteen years. She received MVP, TVP, left atrial maze procedure, and pulmonary vein isolation in age 66. SSS was noticed two weeks after the surgery; thus, a permanent pacemaker was implanted. Hypothyroidism was also noticed during the same hospitalization receiving the surgery. After discharge, she was taking mexiletine 200mg thrice a day, sacubitril 24.5mg/valsartan 25.5mg twice a day, amiodarone 200mg twice a day, warfarin 1mg once a day, and levothyroxine 50mcg once a day. Two years after the surgery, she presented with headache, dizziness, and vomiting for weeks and visited the emergent department due to the symptoms progressed.
Upon physical examination, her temperature was 36.7℃, blood pressure 107/72 mmHg, heart rate 83/min, respiratory rate 18/min, oxygen saturation 96％ on ambient air. Icteric sclera was noticed. Laboratory data showed leukocytosis, abnormal liver function test, and prolonged INR. She was admitted for supportive care. Piperacillin/tazobactam was administered for possible infection.
However, hyperbilirubinemia kept progressing after admission. Extensive workup for etiology, including viral hepatitis serology, autoimmune markers, and abdominal CT scan were unremarkable. Besides, progressive dyspnea also presented during hospitalization, which later required endotracheal intubation and mechanical ventilator support on day 6 after admission. The chest CT demonstrated patchy GGOs

and small patchy consolidation in bilateral lungs with mild fibrotic change and crazy-pavement pattern. Blood, sputum, urine, and bronchoalveolar lavage culture were obtained but later all reported negative. Atypical pathogens included sputum PJP PCR, serum cytomegalovirus viral load, serum aspergillus antigen, serum cryptococcus antigen, and sputum acid-fast stain were also negative. Levofloxacin and anidulafungin were added. Corticosteroid was also administered but hypoxia progressed. She later received CT-guided liver biopsy and VATS lung biopsy.
The pathological examination of liver biopsy tissue showed minimal steatosis with frequent ballooned cell changes and cytoplasmic deposits of Mallory-Denk bodies, diffuse pericellular fibrosis, and neutrophilic satellitosis. The findings featured of steatohepatitis. The differential diagnosis included drug related steatohepatitis, nonalcoholic, and alcoholic steatohepatitis. The lung biopsy tissue revealed chronic interstitial pneumonia associated with diffusely intraalveolar finely vacuolated macrophages aggregation. Fibrinous exudation mixed with polymorphonuclear cells on the pleural surface was noted. The differential diagnosis included drug and smoking related ILD. She did not have alcohol or cigarette usage in the past, and did not take any hepatic and pulmonary toxic drug except amiodarone. Combining history, laboratory, image, and pathology findings, amiodarone induced hepato- and pulmonary toxicity was diagnosed. Amiodarone was discontinued on day 13 after admission. She continued to receive corticosteroid therapy and supportive care, and the condition improved gradually. Nevertheless, a new episode of septic shock presented on day 41 after admission and passed away on day 44 after admission.

Discussion: Chronic amiodarone usage had many potential side effects, hepatic and pulmonary were two of the common one. The severity and clinical relevance of amiodarone induced hepatotoxicity varied widely. It ranged from asymptomatic elevation of liver enzyme levels, to hepatitis, cirrhosis and even hepatic failure. It has been suggested that the risk is related to serum concentration of amiodarone. The characteristic microscopic features of amiodarone induced hepatotoxicity consisted of the changes mimicking those of alcoholic hepatitis, including Mallory body formation, fibrosis, foam cells, ductal proliferation, lipogranulomas, and ballooning degeneration. Most cases with asymptomatic mild enzymes elevation are self-limited and reversible after cessation of amiodarone, but fatal result could still present in those more serious cases. The treatment is mainly supportive. Amiodarone-induced pulmonary

toxicity(APT) is another potential lethal side effect with an incidence of 1.6-2%. Early studies showed mortality of APT was as high as 10-23%. The APT has a broad spectrum and could manifest as many different forms. Risk factors for developing APT included old age(>60 years), male sex, long treatment duration, high cumulative dose, pre-existing lung disease, thoracic surgery, and pulmonary angiography. Risk increased gradually with increasing cumulative dose and reached a plateau in 101-150 gram. Our patient had received amiodarone of 200mg twice daily for 25 months before admission. The cumulative dose exceeded 300gram in total. Other risk factors, including old age and previous thoracic surgery, were also presented in our patient. The gold standard for diagnosis of APT is pathological findings. However, biopsy and pathological examination are not necessary for every patient to diagnose APT. Treatment of APT is discontinuing the amiodarone in mild patients and cessation of amiodarone plus corticosteroid administration in more severe patients. Simultaneous involvement of liver and lung is rare. Due its many possible and potentially lethal side effects, screening and monitoring of some relevant parameters are recommended in patients receiving amiodarone.

Conclusion: Amiodarone is a common, potent, and effective antiarrhythmic drug but carries many significant adverse effects. Early diagnosis of these adverse effects depends largely on highly clinical suspicion and alertness. Hepatotoxicity and pulmonary toxicity are two of the most serious side effects which may require intensive care. In order to minimize the risk, proper maintenance dosage and duration is critical in clinical care. Screening and regular monitoring of the patients who are on amiodarone is also important.