Abstract

Introduction
There are multiple causes of pericardial effusion, including drugs. Avonex® (interferon beta-1a) is an immunomodulator used for the treatment of multiple sclerosis. Adverse cardiac effects associated with the use of Avonex® are exceedingly rare. To date, only one case has been reported by the United States Food and Drug Administration, associating the use of Avonex® with the development of pericardial effusion. We report the second such case.

Case report
A 44-year-old woman with a history of multiple sclerosis, asthma and schizophrenia presented to the Emergency Department with increasing shortness of breath for 2 months, which had acutely worsened that morning, orthopnoea and an unintentional weight loss of 10 pounds over the last 6 months. On examination, the patient was found to be short of breath but haemodynamically stable. Notable findings included bilateral wheezing, jugular venous distension and pulsus paradoxus. An electrocardiogram showed a normal sinus rhythm without electrical alterations. Chest radiograph revealed cardiomegaly; a transthoracic echocardiogram showed a large pericardial effusion with evidence of increased pericardial pressure and impending cardiac tamponade. Additional history revealed that the patient had been started on Avonex® 30 mcg once weekly several months prior. A comprehensive work to exclude all potential causes of pericardial effusion, including connective tissue disorders and infectious aetiologies, proved unrevealing. Surgical drainage was performed. A cytological examination of the pericardial fluid revealed benign mesothelial cells; tissue examination confirmed focal mesothelial hyperplasia. A tuberculin skin test was negative. Computed tomographic scanning of the chest, abdomen and pelvis did not show any evidence of an occult malignancy.

Conclusion
The patient and her neurologist were alerted to the possibility of Avonex®-induced pericardial effusion due to the lack of evidence for other aetiologies. Despite the relative dearth of data on Avonex®-related pericardial effusion, this diagnosis is one that merits consideration to prevent potential morbidity and mortality.

Introduction
Pericardial effusions, often thought to be idiopathic, can be caused by a variety of autoimmune, neoplastic, cardiac, metabolic and infectious aetiologies or can be drug induced. Avonex® (interferon beta-1a) is an immunomodulator approved by the United States Food and Drug Administration (FDA) in 2003 for the treatment of multiple sclerosis (MS). Although Avonex® is not known to have any direct cardiototoxic effects, infrequent reports have emerged linking it to the development of cardiomypathy, congestive heart failure and pericardial effusion. To date, only one case has been reported by the FDA, associating the use of Avonex® with the development of pericardial effusion. Here, we report the occurrence of second such case.

Case report
A 44-year-old woman was admitted to the hospital because of shortness of breath and dyspnoea. Approximately 2 months earlier, the patient had started noticing shortness of breath that had now progressed to dyspnoea on exertion, associated with a drop in exercise tolerance and new-onset orthopnoea.

In the morning on the day of admission, the patient experienced acute worsening of shortness of breath and presented to the hospital.

A detailed history revealed that the patient had a history of schizophrenia, MS and asthma. In addition to the worsening dyspnoea and orthopnoea, the patient also reported an unintentional weight loss of nearly 10 pounds over the course of 6 months. A comprehensive review of all systems revealed no other complaints.

On physical examination, the patient appeared well. The blood pressure was 178/97 mm Hg, the heart rate was 115 beats per minute, the respiratory rate was 22 breaths per minute and the temperature was 97.7°F. There was a pulsus paradoxus of 12 mm Hg (160 mm Hg decreasing to 145 mm Hg on inspiration). The oxyhaemoglobin saturation was determined by pulse oximetry to be 91% while the patient was breathing ambient air. An examination of the woman’s head, eyes, ears, nose and throat showed no abnormalities. An examination of her neck showed a jugular venous pressure of 12 cm H₂O and no lymphadenopathy. Chest auscultation revealed diffuse wheezing bilaterally on auscultation of the lungs. An examination of the heart was remarkable for tachycardia, but revealed no murmurs or pericardial friction rub. Abdominal and neurologic examinations showed

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no abnormalities, and the arms and legs were warm, with symmetric pulses and no oedema. Results of laboratory testing on admission, including thyroid function tests, were unremarkable.

Before proceeding with further diagnostic testing, emergency treatment for acute asthma exacerbation was instituted. Subsequently, a chest radiograph disclosed an enlarged cardiac silhouette (Figure 1) along with evidence of right lower lobe infiltrate. An electrocardiogram showed a normal sinus rhythm at 82 beats per minute and a normal axis; no electrical alternans was seen (Figure 2). A transthoracic echocardiogram showed a large pericardial effusion with moderate right atrial collapse for less than 50% of the cardiac cycle along with early diastolic right ventricular outflow tract collapse (Figure 3). The findings were consistent with increased pericardial pressure.

Additional history revealed that the patient had been diagnosed with MS in 1995 and had been started on Avonex® 30 mcg once weekly (interferon beta-1a) several months prior to this admission. An extensive work-up was initiated to determine the aetiology of the pericardial effusion. Basic laboratory tests, including thyroid function tests and cardiac enzymes, proved unrevealing. Serologic tests were done to exclude viral aetiologies and connective tissue disorders. A viral panel consisting of parvovirus, Epstein–Barr virus, cytomegalovirus, Coxsackie virus and hepatitis serologies, influenza flu swab and tests for human immunodeficiency virus infection were negative. Additional testing for antinuclear antibody and extractable nuclear antigen antibody panel, erythrocyte sedimentation rate, C-reactive protein and rheumatoid factor panel were all found to be unremarkable.

The patient was taken to the operating room (OR) for surgical drainage of the effusion. In the OR, 600 cc of serous pericardial fluid was evacuated. A catheter drained decreasing amounts of fluid during the next 48 h and was subsequently removed.

A cytological examination of the pericardial fluid showed red blood cells and benign mesothelial cells but no malignant cells. A Gram’s stain of the pericardial fluid failed to reveal the presence of any neutrophils or organisms. Bacterial and fungal cultures did not show any growth. Histopathological examination of the pericardial window tissue examination revealed only pericardium with focal mesothelial hyperplasia. A smear and culture were negative for acid-fast bacilli and mycobacteria.

Figure 1: 12-lead electrocardiogram shows a normal sinus rhythm at 82 beats per minute, a normal axis and no electrical alternans.

Figure 2: Chest radiograph showing enlarged cardiac silhouette.
Blood, urine and sputum cultures, which were sent out on admission, did not show any growth in the subsequent days.

The finding of red blood cells in the pericardial fluid cytological examination, coupled with the patient’s history of unintentional weight loss, raised the concern for the presence of an occult malignancy. However, a postoperative computed tomographic (CT) scan of the chest, abdomen and pelvis performed with intravenous contrast was unremarkable for abnormalities. An injection site examination and pericardial fluid cytological examination were reported during premarket and post-market evaluation of the drug. Figure 3: The apical four-chamber view shows a large pericardial effusion (PE), diastolic collapse of the right atrium (RA) and the right ventricle (RV). LA, left atrium; LV, left ventricle.

Discussion

The normal pericardium is an avascular fibroelastic sac that surrounds the heart. It consists of the visceral and parietal pericardium, separated by a potential space that can normally contain 15–35 ml of serous fluid. Pericardial effusions result when the intrapericardial fluid volume exceeds its physiological limit; it may develop acutely or slowly over time resulting in subacute or chronic pericardial effusions.

The aetiology of pericardial effusions is variable. Pericardial effusions can be secondary to acute pericarditis (90% of which are idiopathic or viral). Other causes that merit consideration include bacterial, rickettsial, viral and protozoan infections, tuberculosis, uraemia, cholesterol, myxodema, neoplasms, myocardial infarction, cardiac surgery, trauma, drugs and autoimmune diseases including collagen vascular diseases and sarcoidosis. While the frequency of causes of pericardial effusions may vary geographically, in several case series the aetiology of moderate-to-large pericardial effusions was found to be idiopathic in most cases.

Drug-induced pericardial effusions remain an important consideration when searching for the aetiology of pericardial effusions. Drugs that have been associated with the development of effusions include, but are not limited to, hyaluridase, phenylbutazone, tetracycline, streptomycin, methylichenouracil (not used in the United States), procainamide, isoniazid, dantrolene, cromolyn sodium, methysyergide, anticoagulants, phenytoin, penicillin and doxorubicin. Avonex® (interferon beta-1a, Biogen, Cambridge, MA, USA) is an immunomodulator approved by the FDA for the long-term treatment of relapsing–remitting MS. Interferon beta-1a is a glycosylated mammalian cell product produced by recombinant DNA technology, with an amino-acid sequence identical to that of natural human beta interferon. It is administered intramuscularly once a week as a 30 mcg dose. The side effect profile includes injection site reactions, flu-like symptoms, menstrual disorders, depression, laboratory abnormalities including cytopenias and elevated levels of transaminases. Although Avonex® is not known to have any direct cardiotoxic effects, adverse effects on the cardiovascular system were reported during premarket and post-market evaluation of the drug. The side effects that have been listed include the development of cardiomyopathy and congestive heart failure in patients with no prior history of cardiac disease. Notably, pericarditis has also been listed as an adverse effect associated with the use of Avonex®.

According to the data reported on the eHealthMe.com website, on 8 February 2013, 97,951 people reported experiencing side effects when taking Avonex®, of which 0.12% reported to have developed pericardial effusion.
To date, only one case has been reported by the FDA, associating the use of Avonex® with the development of pericardial effusion17. A 63-year-old woman developed pericardial effusion and subsequently required hospitalization for management. Avonex® was implicated as the primary culprit associated with the development of the pericardial effusion.

The presence of pericardial effusions should be suspected based on the history, physical exam and electrocardiographic findings. Although the relatively inelastic properties of the pericardium limit the amount of fluid that can be accommodated, slowly developing effusions allow for pericardial stretch and the activation of compensatory mechanisms with the result that the intrapericardial volume can rise up to 2 l or more without the development of acute symptoms18. Patients with subacute tamponade may remain asymptomatic or complain of chest discomfort, fatigue and other symptoms related to impaired cardiac function. Physical signs associated with the presence of effusions are often nonspecific18,19.

It is likely that in the case of our patient, the pericardial effusion had accrued over time, leading to symptoms of cardiac dysfunction and clinical presentation of impending tamponade.

Cardiac perforation, on the other hand, can result in rapid intrapericardial haemorrhage and development of acute cardiac dysfunction, secondary to limitation of cardiac inflow.

Once the pericardium has been stretched to its limit, further increases in the intrapericardial volume can cause a critical rise in the pericardial pressure to the point where cardiac tamponade results.

Cardiac tamponade is a life-threatening condition caused by the slow or rapid compression of the cardiac chambers to the point where cardiac filling is altered, resulting in impaired cardiac output. Critical tamponade is the decompensated phase of cardiac compression that can lead to cardiogenic shock and is rapidly fatal if unrecognized. Hence, cardiac tamponade merits consideration in the differential diagnosis of patients with shock or pulseless electrical activity20.

Patients with early or impending tamponade appear anxious and may complain of chest pain and dyspnea18. The increased venous pressure is apparent on physical exam as jugular venous distension; exceptions include ‘low-pressure’ tamponade seen in hypovolemic patients, such as those with rapidly developing haemorrhagic tamponade. Pulsus paradoxus21, defined as an inspiratory systolic drop in the arterial pressure by >10 mm Hg during normal breathing, is the hallmark of cardiac tamponade. Although cardiac tamponade is considered a clinical diagnosis, all cases of suspected cardiac tamponade should be evaluated with an electrocardiogram, chest radiograph and echocardiography.

Enlargement of the cardiac silhouette on chest films with clear lung fields is suggestive of pericardial effusion; however, at least 200 ml of fluid must be present before the cardiac silhouette is affected. In lateral films, pericardial-fat lines, if present, are considered highly specific for large effusions19.

Electrocardiographic changes include sinus tachycardia, signs of pericarditis and electrical alternation. In some cases, large pericardial effusions, even in the absence of tamponade, can cause QRS alternation22. Combined P and QRS alternation in a patient with normal sinus rhythm is considered virtually pathognomonic for tamponade23.

Doppler echocardiography is a key tool in the evaluation of pericardial effusion and should be performed in cases of suspected tamponade without delay23.

Among the echocardiographic signs, the most characteristic one is the collapse of the cardiac chambers, nearly always of the RA (right atrium) and RV (right ventricle). RA collapse, especially when it persists for more than one-third of the cardiac cycle, is highly sensitive and specific for cardiac tamponade. In contrast, brief RA collapse can occur in the absence of cardiac tamponade24. RV diastolic collapse is less sensitive for the presence of cardiac tamponade than RA diastolic collapse, but is very specific for cardiac tamponade20,25,26.

The treatment of cardiac tamponade is drainage of the pericardial contents, which can be achieved by needle pericardiocentesis25 or through surgical drainage. Medical management remains controversial27. Pericardiocentesis can be performed under image guidance with the use of echocardiography23 or CT. Non-emergent drainage can also be performed in the catheterization laboratory under fluoroscopic guidance28 and is particularly useful when the diagnosis is unclear, and to detect effusive constrictive pericardial disease. However, cardiac tamponade with overt haemodynamic compromise requires urgent pericardiocentesis even without imaging, since it is only the removal of the pericardial fluid that produces rapid cardiac and haemodynamic improvement29.

Surgical drainage is preferable in patients with intrapericardial bleeding and in those with clotted haemopericardium or thoracic conditions that make needle paracentesis ineffective10. Surgical drainage also allows for the biopsy of the pericardium, and the advent of flexible pericardiocopy30, has served to enhance the diagnostic accuracy. Recurrent pericardial effusions, particularly in patients with malignant tamponade, may require the creation of a pericardial window, surgically or by balloon dilation30, to prevent the recurrence of cardiac tamponade.
byallowing the effusion to drain into the pleural or peritoneal space.1,18.

Conclusion
Our patient underwent an exhaustive work-up to determine the aetiology of the pericardial effusion. However, the process of elimination ruled out all other potential causes. The most plausible cause of pericardial effusion in this case appeared to be an adverse reaction related to the use of Avonex®.

Despite the relative paucity of data on Avonex®-related pericardial effusion, this diagnosis, albeit of one exclusion, is one that must be promptly recognized in order to avoid potential morbidity and mortality.

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations list
CT, computed tomographic; FDA, Food and Drug Administration; MS, multiple sclerosis; OR, operating room.

References

Case report

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