Severe Pleuropericarditis and Cardiomyopathy Induced by High Dose Interferon alpha-2b

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High dose interferon alpha-2b is used as adjuvant therapy for cutaneous melanoma and has been shown to have a reproducible benefit [1]. The drug has many side effects, of which constitutional flu-like symptoms are the most prevalent. A multitude of other adverse effects have been described involving every major organ system. Cardiotoxity is rare and previous reports have described various arrhythmias, cardiomyopathy and ischemic heart disease.

We report a case of severe cardiotoxicity during treatment of melanoma with high dose IFNα-2b. This potentially lethal effect reversed upon cessation of interferon and steroid administration.

Patient Description

A 63 year old man was admitted to the department of internal medicine because of dyspnea, weakness and left pleuritic chest pain that appeared 2 days prior to admission. According to his history, 22 years previously he had undergone splenectomy and removal of a tumorous mass involving the stomach, which was diagnosed as diffuse large B cell non-Hodgkin's lymphoma. A full course of chemotherapy consisting of cyclophosphamide, adriamycin, vincristine and dexamethasone (CHOP) was administered. The total cumulative dose of adriamycin was 400 mg/m^2. Radiotherapy was not administered. He had been in remission ever since. He had no cardiac history other than an insertion of a permanent pacemaker due to symptomatic fascicular block of unknown etiology 6 months before the current presentation. A recent echocardiography revealed normal systolic function. He had been asymptomatic since the pacemaker insertion.

A malignant melanoma involving the left inguinal lymph nodes was diagnosed 3 months before presentation. The primary site was not identified in spite of careful investigation. After excision of the inguinal nodes, he received high dose IFNα-2b (18 x 10^6 units per day intravenously) for 1 month. No other medications were administered. The interferon treatment was suspended a week before his admission due to elevated liver enzymes. Radiotherapy directed to the left inguinal area alone was started 2 weeks prior to the current admission.

On physical examination he was afebrile but looked sick and was tachypneic and hypotensive (85/55 mmHg). Breathing sounds were diminished bilaterally and percussion was dull. A third heart sound was heard over the precordium as well as a pericardial friction rub. Noteworthy laboratory results included a white blood cell count of 15,000/mm^3 with left shift, a sedimentation rate of 40 mm/hour and presence of antinuclear antibodies (titer 1/40). All other values were within normal range. The ECG did not show signs of ischemia or hypertrophy. A chest X-ray showed an enlarged heart silhouette and bilateral pleural effusion. Transthoracic echocardiography demonstrated severe global systolic dysfunction, moderate mitral regurgitation, and a pulmonary artery pressure of 50 mmHg but no pericardial fluid.

The pleural effusion was aspirated. It was an exudate with abundant inflammatory cells and the pH was 7.4. There were no malignant cells. Chest and abdominal computerized tomography scan did not disclose any metastatic spread. The patient was treated with dexamethasone, atenolol and furosemide. Within a few days all symptoms and signs of congestive heart failure resolved and the friction rub disappeared. No pleural effusion was noted on a subsequent chest X-ray. A repeat echocardiography performed 8 weeks later revealed mild-to-moderate left ventricular dysfunction and mild-to-moderate mitral regurgitation.

Comment

Cardiac toxicity due to interferon is uncommon and the literature survey yielded only small case series and case reports. The most commonly reported adverse effects are transient hypotension upon initiating treatment, atrial extasystoles, and other supraventricular arrhythmias that are generally benign. Less commonly, various conduction abnormalities were described [2]. Serious cardiotoxicity is rarely reported and includes lethal arrhythmias, dilated cardiomyopathy and myocardial infarction. Our patient is unique since he presented with both congestive heart failure (S_3 and global left ventricular dysfunction) and inflammation (pericardial friction rub and exudative cellular pleural effusion).

There are no established predisposing factors for interferon cardiotoxicity. Patients with previous heart disease are probably at higher risk for arrhythmia and ischemic manifestations [3], but not for cardiomyopathy. IFNα is the most cardiotoxic of the three interferons, followed by IFNγ and IFNβ. Toxicity does not depend on the daily dose, the total amount, or the duration of treatment.

It is plausible, but not established, that

IFNα = interferon alpha

radiotherapy and other cardiotoxic agents predispose patients to higher rates of interferon cardiotoxicity. It is possible that our patient had subclinical doxorubicin-induced cardiac disease which exposed him to the adverse effects of interferon. However, since the cardiotoxicity was reversible, and the fact that the total dose of doxorubicin was below the cardiac toxic range, and that it was administered 20 years earlier suggest that interferon was the major cause of the cardiac damage.

The mechanism of interferon cardiotoxicity is unclear and is probably multifactorial. Experimental infusion of recombinant IFNα may cause arrhythmia and ischemia. There is evidence that interferon may damage endothelial cells, cause the thickening of capillary walls, and induce deposition of immune complexes. Interferon evokes the release of several cytokines, including tumor necrosis factor alpha, and interleukins 2, 6 and 1, affecting autonomic sympathetic nerve activity and vasopressor responses [4]. Interferon has been associated with exacerbation or induction of a wide variety of clinical and serological immune disorders, including systemic lupus erythematosus, rheumatoid arthritis, autoimmune hepatitis, thyroid disease and diabetes mellitus. There is only a single report of autoimmune pericarditis that was not accompanied by congestive heart failure.

Treatment of interferon-induced cardiotoxicity rests mainly on early recognition and drug discontinuation. There is a high degree of individual variation in toxicity, but most adverse events are reversible upon cessation of the drug. Arrhythmia, ischemia and congestive heart failure are treated with standard measures. Since the cardiac symptoms occurred 1 week after discontinuation of the drug and were associated with an inflammatory response, we decided to add steroids to the treatment. Indeed, within several days a dramatic improvement, both subjective and objective, was noted. For causality assessment, we used the Naranjo ADR Probability Scale, a validated tool used to determine the likelihood that the adverse drug reaction is caused by the implicated medication. The Naranjo algorithm requires a series of questions to be answered and scored. The total calculated score indicates the likelihood – from doubtful, possible, and probable to highly probable – of causing an adverse drug reaction. The appearance of cardiomyopathy and pleuropericarditis after the administration of high dose interferon, and the prompt improvement in the patient's condition after the drug was discontinued without an alternative explanation for this adverse event, yielded a total score of +5 (range -4 to +13) on the Naranjo ADR Probability Scale and indicate a probable relationship [5].

In summary, we report a patient with no significant history of myocardial dysfunction who developed a clinical and echocardiographic picture of cardiomyopathy and pleuropericarditis after treatment with high dose interferon. It highlights previously unreported inflammatory-type adverse cardiac effects of high dose interferon, which are reversible and responsive to steroid treatment.

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