

CASE STUDY

Lone Atrial Fibrillation: More Than Meets the Eye

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Doxorubicin has been used as a chemotherapeutic agent for over 30 years. Its cardiac toxicity has been known for over 20 years. In recent years, delayed-onset cardiac toxicity has been described as yet another cardiac complication of doxorubicin and other anthracyclines. The following case is felt to represent such an example.

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R. D. is a 40-year-old white, married male who applied for \$1,000,000 of term life insurance in October 2003. He is vice president of a family-owned company. On the application, his height was 6'3", and his weight was 225 lbs. He denied tobacco use and he drank alcohol rarely. He was admitted for a 1-day hospital stay in June 2003 for atrial fibrillation. His only currently listed medication was metoprolol XL 50 mg per day.

Medical records from 1998 to the present revealed the following visits and data:

- Fall 1998. He was seen for seasonal allergies. BP-108/82.
- February 2002. He had an unremarkable complete physical exam. Note was made of a history of rhabdomyosarcoma 20 years prior. BP-112/74; cholesterol 177 mg/dL, HDL 50 mg/dL, triglycerides 108 mg/dL; HIV (-); Hep B surface antigen (-); Hep C antibody(-).
- September 2002. Visit for seasonal allergy injection: triamcinolone.
- May 2003. Emergency room visit for conjunctivitis and allergies, treated with fexofenadine. BP recorded:129/72.

- June 2003. Chief complaints: palpitations, weakness, fatigue. He was found to be in acute atrial fibrillation and admitted to the hospital to rule out an acute MI. While being rolled via cart to his room, he converted to normal sinus rhythm. At no time did he have chest pain. He was treated with metoprolol and enoxaparin. On admission, pulse was recorded as 110–140 bpm, irregular, BP recorded as 115/77. His lungs were clear, no murmur was heard, and he had no peripheral edema.

Cardiac evaluation found: ECG-rapid atrial fibrillation, S1S2S3 axis, slow R wave progression V2-4. Echocardiogram showed normal chambers, valves, pulmonary pressure; EF-50–55%, globally at lower limits of normal, LVEDD = 4.8 cm, aortic root = 4.4 cm, LA = 3.5 cm, IVS = 1.1 cm, LVPW = 1.0 cm. Chest x-ray showed borderline cardiomegaly. Laboratory results included: ESR = 6 mm/hr; LDH = 359 U/L; CPK = 155 U/L; Troponin I <0.3 ng/ml; (all 4 test results were normal).

Additional history given in the cardi-

ology consult revealed a prior history of a rhabdomyosarcoma in 1984. He received doxorubicin and had acute atrial fibrillation following one injection of doxorubicin that resolved promptly. He had cardiology follow-up including echocardiograms. He was told that his heart was normal and he did not need additional follow-up.

- June 2003. At an office visit one week after discharge from the hospital, he was taking metoprolol XL 50 mg/d, and switched from fexofenadine to loratadine for his allergies. He avoided ephedrine and decreased his caffeine intake. Vital signs recorded were pulse = 72 and regular, BP = 110/64.
- July 2003. A stress ECG was stated to be negative. His exercise duration was greater than 10 minutes. His pulse rate was noted to be >100 five minutes after exercise on metoprolol therapy. The cardiology diagnosis was lone atrial fibrillation probably related to doxorubicin cardiotoxicity.
- October 2003. Date of application for life insurance.

CASE DISCUSSION

The mortality concerns in the case are the acute atrial fibrillation and the apparent doxorubicin-induced cardiomyopathy.

The questions raised are whether the mortality concerns are related and whether there are long-term mortality studies on doxorubicin-induced cardiotoxicity.

The anthracyclines, of which doxorubicin is a prototype, have been used as very effective anti-neoplastic agents for over 30 years.^{1,3} Their cardiac toxicity has been known for over 20 years. Both the anti-neoplastic efficacy and the toxicity are dose related. The anthracyclines are the leading cause of chemotherapy-induced heart disease.²

The exact mechanism of the anti-neoplastic activity of the anthracyclines is unknown. It is felt to be due to two factors. First, the anthracyclines intercalate with nucleotide bases

in the DNA that indirectly inhibits Topoisomerase II, which is a mechanism of cytotoxic activity. Second, the anthracyclines chelate iron, which in turn generates extremely toxic hydroxyl (OH) free radicals that appear to play a role in cytotoxic activity.

The exact cause and pathogenesis of the cardiac toxicity are also unknown. Specific pathological changes that occur include myofibrillar loss and dilatation and vacuolization of the sarcoplasmic reticulum.⁴ An experienced pathologist may be needed for correct interpretation of the biopsy specimen. Because endocardial biopsy is an invasive procedure and subject to sampling error, it is not commonly performed during the phase following anthracycline chemotherapy.

There are four subsets of anthracycline-induced cardiac toxicity (Table 1).

The chronic cardiomyopathy related to anthracycline use is directly-dose related (Table 2). A total dose of <550 mg/m² is the current recommendation for doxorubicin administration. However, there is wide individual variation in sensitivity to doxorubicin. Doses as small as 183 mg/m² have caused changes on biopsy, and doses as large as 1000 mg/m² have been tolerated. Risk factors for the development of the cardiomyopathy are debated, but are generally accepted to include: 1) large doses of doxorubicin, 2) prior mediastinal radiation, 3) rapid infusion of doxorubicin, 4) young or advanced age, and 5) female gender.

Current recommendations to avoid the chronic cardiomyopathy are to give lower amounts of doxorubicin, infuse doxorubicin slowly over 48–96 hours, and use simultaneous antioxidant therapy (Dextazoxane).⁵

The delayed-onset cardiomyopathy has been recently recognized as more survivors of childhood malignancy and anthracycline treatment reach adulthood. In one study, up to 38% of such patients had occult left ventricular dysfunction and another study found 3% to 5% of patients had nonsustained ventricular tachycardia. The natural history of the LV dysfunction and the arrhythmias remains to be elucidated. There are currently no

Table 1. Anthracycline-induced Cardiac Toxicity Subsets

Subtype	Frequency	Onset	Clinical Characteristics
1. Acute	Rare	Immediately after injection	Vasodilatation, hypotension, non-specific ST-T changes on ECG, arrhythmias
2. Subacute	Rare	Immediately after injection	Pericarditis, myocarditis, acute left ventricular failure
3. Chronic cardiomyopathy	More common, dose related	Within one year after treatment	Congestive heart failure (CHF)
4. Delayed-onset cardiomyopathy	Common	>one year after treatment; can be >15 years after treatment	Occult left ventricular dysfunction, CHF, sudden death, arrhythmias

Table 2. Chronic Cardiomyopathy

Cumulative Dose of Doxorubicin	% of Patients with CHF
<400 mg/m ²	0.14
550 mg/m ²	7
700 mg/m ²	18

guidelines for chronic monitoring of this subset of patients.

CASE COMMENT

Although our applicant was diagnosed as a lone atrial fibrillation, it is apparent that he is in the subset of delayed-onset cardiomyopathy secondary to treatment with doxorubicin for his rhabdomyosarcoma 20 years prior. There are no mortality studies to help us sort out his mortality risk. In his favor is the long duration of time to onset of arrhythmia and the low normal ejection fraction on echo.

It appears that he will have ongoing follow-up care. I concluded that a high mortality ratio was present in this case.

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REFERENCES

1. Shan K, Lincoff A, Young JB. Anthracycline-induced Cardiotoxicity. *Ann of Int Med.* 1996;125(1): 47-49.
2. Smith A, Schlant R. Effects of noncardiac drugs electricity, poisons, and radiation on the heart. *Hurst's The Heart, Arteries and Veins.* 9th ed. 1998; 2153-2155.
3. Richardson D, Johnson S. Anthracyclines in haematology: preclinical studies, toxicity and delivery systems. *Blood Rev.* 1997;11(4):201-223.
4. Ferrans V, Clark J, Zhang J, Yu ZX. Pathogenesis and prevention of doxorubicin cardiomyopathy. *Tsitologiya.* 1997;39(10):928-937.
5. Iarussi D, Indolfi P, Casale F, Coppolino P, Tedesco M, Di Tuljio M. Recent advances in the prevention of anthracycline cardiotoxicity in childhood. *Curr Med Chem.* 2001;8(13):1649-1660.