

## Case Report: Management of cardiotoxicity in a survivor of acute lymphocytic leukemia

### Abstract:

A 22-year-old male who is a survivor of acute lymphocytic leukemia presented for a regular check up by his family doctor. His most recent echocardiogram showed a borderline systolic function with an ejection fraction of 50-60%. Part of the patient's treatment for acute lymphocytic leukemia included anthracycline antibiotics, which are known to cause cardiotoxicity.<sup>1</sup> The clinical question arose of what the family doctor should monitor for in a patient exposed to anthracycline antibiotics, as well as if any medical intervention was necessary at that time. A literature review revealed that the incidence of congestive heart failure in childhood cancer survivors exposed to anthracycline antibiotics was 1.7%.<sup>2</sup> However, there is no consistent agreement in the literature about the incidence of subclinical cardiomyopathies and their management. Nevertheless, with an ejection fraction above 50%, no medical intervention is required. Instead, care for the patient should be focused on reducing cardiac risk factors and managing hypertension if it is present.<sup>3</sup> Some studies have shown that aerobic exercise can also improve ejection fraction in these patients.<sup>4</sup>

### Background:

Although Acute Lymphocytic Leukemia (ALL) is the most common type of childhood cancer, it is still relatively rare with an incidence rate of 3.4 cases per 100,000 in the United States. ALL is more common in children than in adults, with peak age of diagnosis falling between two and five years of age. The cure rate for ALL is 85% in the United States.<sup>5</sup>

Despite having a high cure rate, treatment for childhood leukemia often leaves lasting effects. Survivors of ALL are at increased risk of cardiac toxicity, central nervous system impairment, secondary neoplasms, metabolic dysfunction and decreased fertility, among others. One of the more well-known side effects of the treatment is cardiac toxicity leading to cardiomyopathies. In some individuals, the cardiomyopathies lead to congestive heart failure and early death.<sup>5</sup>

Adequate management and follow-up care for the survivor of acute lymphocytic leukemia is essential. Many of these risk factors have improved outcomes with adequate monitoring and early intervention. Thus, the onus falls on the family doctor to understand and regularly check for the side effects.<sup>1</sup>

### Case Description:

A 22-year-old male became a new patient of a rural family medicine practitioner. In 2006, the patient was diagnosed with high-risk acute lymphocytic leukemia, and has been followed at Cancer Care and by his family doctor ever since. His previous family doctor moved provinces, so he presented to his new family doctor with an extensive medical history.

His cancer was diagnosed in 2006 when he presented to the Boundary Trails emergency room with a swollen face and shortness of breath. An X-ray showed a mediastinal mass and he was found to have superior vena cava syndrome. He was transferred to the Children's Hospital

where a biopsy of the mediastinal mass demonstrated he had Acute Lymphocytic Leukemia. Over the next eight years, the patient received chemotherapy and radiation therapy. Medical treatment included twelve different chemotherapy agents including corticosteroids, plant alkaloids, anthracycline antibiotics, enzymes, antimetabolites and alkylating agents. The patient also received prophylactic cranial radiation.

Now, his cancer has been in remission for eight and a half years. A note in his file from the pediatric oncologist asks the family doctor to monitor TSH, T4 and do yearly thyroid exams, blood pressure checks, skin exams, and have an echocardiogram done annually.

On exam, the patient's blood pressure was 133/80, his thyroid was normal, as was his cardiac exam, skin exam and all blood work. His most recent annual echocardiogram showed a mildly dilated left ventricle with an ejection fraction of 50-60 percent and a mildly enlarged right ventricle with normal systolic function. His overall left ventricular systolic function was classified as borderline/normal.

This case was chosen because of the rarity of the condition and the importance of the follow-up management by the family doctor. At the time of the patient's presentation at the clinic, there was a discussion of what should be looked for on exam in relation to the potential cardiomyopathies, as well as what the outcome for this patient is likely to be.

#### Literature Review:

The clinical question in this case is what red flags the clinician should be looking for on history and exam in relation to cardiotoxicity, and how the clinician should manage the echocardiogram results. A literature review was performed to investigate the cardiotoxic effects of "ALL high-risk COG protocol" that the patient received. The literature review began by looking up the chemotherapy treatments that the patient received in the Child Oncology Group (COG) Survivorship Guidelines that is referenced in the patient's chart. This provided the guidelines for management of someone exposed to anthracyclines.

Next, Up To Date was used to understand the epidemiology of ALL as well as the mechanism and follow up guidelines of someone with anthracycline-induced cardiotoxicity.

Finally, to better understand the different etiologies of cardiotoxicity associated with anthracyclines, a PubMed search was done using the term "childhood leukemia long-term side effects" and "cardiotoxicity after anthracycline use," as well as "subclinical cardiomyopathies after anthracycline" This yielded five articles of interest.

#### Discussion

There are many potential long-term sequelae associated with the treatment for ALL. Because of the recent findings on the echocardiogram, the discussion will be focused there. The clinical question will focus around what cardiotoxicities are associated with ALL treatment, how they should be monitored, and any interventions required.

Cardiotoxicity is a long-term side effect because of the use of anthracyclines in the treatment of ALL. In this case, the patient received Daunorubicin and Doxorubicin totalling 158.3 mg/m<sup>2</sup>. This is considered low dose, as it is less than 300mg/m<sup>2</sup>.<sup>6</sup>

According to the COG Survivorship guidelines, anthracycline antibiotics have been linked with cardiomyopathies, arrhythmias and subclinical left ventricular dysfunction.<sup>6</sup> There are different theories about the mechanism of cardiac toxicity. However, it has been established that reactive oxygen species formation followed by myocyte damage plays a role, as well as apoptosis through DNA damage.<sup>3</sup>

Different risk factors that are associated with increased likelihood of anthracycline-induced cardiotoxicity include the dose of anthracycline received, being of African descent, being under the age of five when the medication is given, radiation involving the heart area as well as other risk factors that predispose individuals to cardiac failure like smoking, obesity and hypertension.<sup>3</sup> Of these risk factors, our patient had none.

The most common manifestation of the use of anthracyclines are cardiomyopathies, often leading to impaired systolic and diastolic heart function and ultimately congestive heart failure.<sup>1</sup> One study showed that for children diagnosed with ALL between the years of 1992-2010 (which our patient was) in Ontario had an incidence of congestive heart failure of 1.7% ten years after diagnosis.<sup>2</sup> Nevertheless, the dose of anthracyclines given was a large contributing factor. One study even found that in individuals where the anthracycline dose was under 270 mg/m<sup>2</sup> no cardiac abnormalities were found.<sup>1</sup>

However, in the current case study, the result of the patient's echocardiogram was borderline/normal, suggesting that this patient has subclinical cardiomyopathies twelve years after diagnosis. There was found to be more discrepancy in the literature about the incidence and outcome of subclinical cardiomyopathy. A systematic review done in 2002 that looked at 25 studies found that subclinical cardiotoxicity (defined as abnormal systolic function or abnormal afterload) ranged between 0% and 57%.<sup>7</sup>

This then begs the question of how to manage the patient. Both of the patient's ventricles are dilated, and his ejection fraction is estimated to be between 50-60%. The patient is asymptomatic. According to the COG Survivorship Guidelines, there should be yearly exams where a cardiac history and exam are done, as well as an echocardiogram and EKG done yearly.<sup>6</sup> At the most recent visit, the patient's cardiac exam was normal, and there were no red flags on history.

According to Up to Date, it is important to initiate therapy with a beta blocker and ACE inhibitor as soon as a patient's ejection fraction falls below fifty percent. Currently, the Canadian guidelines for heart failure management suggest considering starting an ACE inhibitor and beta blocker in patients with an ejection fraction greater than 40 percent only if they are symptomatic. However, in the case of a patient with anthracycline-induced cardiotoxicity, Up to Date states that beta blockers and ACE inhibitors have been shown to prevent further deterioration.<sup>3</sup> The study cited by Up To Date was a prospective cohort study. They found that initiating beta blockers and ACE inhibitors in patients with ejection fractions <50% resulted in improvement in cardiac function. 25% had complete return of ejection fraction to baseline, while the other 75% showed partial recovery (EF >50%).<sup>8</sup>

The COG Survivorship Guidelines say that patients treated with anthracycline antibiotics should avoid heavy weight lifting and isometric activities.<sup>6</sup> However, one study suggests that

patients can benefit from aerobic and strength training. The study involved five patients who were minimum ten years post diagnosis of cancer and had ejection fractions between 40 and 55 percent. Over the course of twelve weeks, the patients completed aerobic and resistance training. On average, the ejection fraction of the patients improved 12.6. The conclusions drawn from the study state that these results are consistent with other studies that have also found that aerobic training can improve ejection fraction in patients with dilated cardiomyopathies. However, the authors recognize that their sample size was small and that other factors could have contributed to the results, and conclude that more research needs to be done in this area.<sup>4</sup>

Returning to the case at hand, since the patient's ejection fraction remained above 50 percent, beta blockers or ACE inhibitors are not yet required. Rather, management is focused on controlling hypertension if it becomes present and monitoring and counselling about other cardiac risk factors such as smoking and exercise.

## Conclusion

This case represented a unique clinical question for a rural family doctor. The relative rarity of childhood leukemia and the findings on echocardiogram meant that management of this patient required knowledge of the side effects and long-term sequelae of anthracycline antibiotics.

At 1.7% after ten years, the incidence of congestive heart failure in those exposed to anthracycline antibiotics remains low.<sup>2</sup> More research needs to be done to determine the rate of subclinical cardiomyopathies, like the ones present in our case.<sup>1</sup>

The literature suggests that at the present time there is no medical management required for the patient, however close monitoring should be pursued and therapy initiated if his ejection fraction falls below 50%.<sup>3</sup> Furthermore, the patient's ejection fraction might improve with aerobic exercise.<sup>4</sup>

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