CASE REPORT

Hypothyroid cardiomyopathy in a patient post-doxorubicin chemotherapy

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SUMMARY

Hypothyroidism may cause decreased cardiac output and heart failure—and when severe, bradycardia and pericardial effusions may develop. Chemotherapies, particularly doxorubicin, are known and often irreversible causes of cardiomyopathy. As such, when cardiomyopathy develops in patients who have been exposed to anthracycline chemotherapy, the importance of ruling out other reversible causes such as hypothyroidism cannot be overstated. We present a case of acute systolic heart failure in a patient post-doxorubicin chemotherapy and radiation therapy for alveolar rhabdomyosarcoma, found to have severe hypothyroidism as a reversible cause of cardiomyopathy.

BACKGROUND

Recognising secondary causes of cardiomyopathy is of particular clinical importance as cardiovascular disease may be reversible with treatment of the underlying condition. Hypothyroidism exemplifies a secondary aetiology of cardiomyopathy that causes decreased cardiac output and heart failure. There are no reports to date of cardiomyopathy due to severe hypothyroidism among patients exposed to doxorubicin-based chemotherapy regimens. This case underscores the importance of screening for reversible causes of cardiomyopathy, even in patients with a known alternative explanation such as anthracycline chemotherapy.

CASE PRESENTATION

A 29-year-old man presented to our Cardio-oncology clinic at Rush University Medical Center, for a second opinion of presumed acute systolic heart failure secondary to chemotherapy-induced cardiotoxicity. He presented with persistent fatigue, intermittent diarrhoea, light-headed dizziness, face and neck swelling, hoarse voice and stable weight. Two-dimensional Doppler transthoracic echocardiogram (TTE) at that time demonstrated left ventricular ejection fraction (LVEF) 35–40%, a small anterior pericardial effusion (figure 1A, 1B, 1C, 1D), with moderate diffuse hypokinesis (figure 1E) and abnormal global longitudinal peak strain at –11% (figure 1F). The patient had a medical history of stage 4 alveolar rhabdomyosarcoma diagnosed at the age of 28 years and was enrolled in an experimental trial of aggressive anthracycline-based therapy. At the time he presented to our clinic, he had received a life-time exposure of 350 mg/m² of doxorubicin. Apart from the rhabdomyosarcoma, he denied any specific medical history. His family history was significant for hypothyroidism in his

maternal and paternal grandmothers and thyroid cancer in his paternal uncle. Physical examination was unremarkable.

Laboratory data showed an elevated thyroid-stimulating hormone (TSH) of 157.8 µIU/mL (0.34–4.940 µIU/mL). On further specific questioning, the patient reported that, at the age of 13 years, he had been diagnosed with hyperthyroidism, for which he took antithyroid medications for 4 years, but was then lost to follow-up until his diagnosis of rhabdomyosarcoma. At this point, he was referred to endocrinology and initiated on weight-based levothyroxine dosing at 137 mg/m² daily. At 6-week follow-up, his heart failure symptoms had resolved and his TSH had declined to 20.6 µIU/mL. Surveillance TTE showed interval improvement of LVEF to 50%, resolved anterior pericardial effusion (figure 2A–E) and global longitudinal strain normalisation to –19% (figure 2F). Levothyroxine was uptitrated; 4 and 9-month surveillance TTEs demonstrated improved EF to 55–60% and 60–65%, respectively. His global longitudinal strain parameters remained normal. These objective data corresponded with significant symptomatic improvement and return to normal functional status.

DISCUSSION

Hypothyroidism—whether overt or subclinical—is a multifactorial risk factor for reversible cardiovascular disease.^{1 2} It is specifically associated with increased systemic vascular resistance, increased C reactive protein, decreased cardiac contractility, decreased cardiac output, accelerated atherosclerosis and coronary artery disease.² The mechanism by which hypothyroidism leads to cardiovascular disease is explained by Danzi and Klein. Triiodothyronine (T3), the physiologically active form of thyroid hormone, binds to nuclear receptor proteins that mediate cardiomyocyte gene expression. T3 in turn mediates vascular smooth muscle relaxation thereby decreasing arterial resistance and diastolic blood pressure. Whereas in hyperthyroidism, cardiac contractility and cardiac output are enhanced, hypothyroidism manifests as impaired LV systolic function and impaired myocardial strain due to increased afterload.^{2 3}

The recognition of hypothyroidism as a cause of LV dysfunction is of particular importance to clinicians, given the reversibility of cardiovascular disease due to underlying hypothyroidism. It has long been shown that appropriate thyroid hormone replacement can restore LV function and even reverse pericardial effusions caused by

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Figure 1 Transthoracic echocardiogram findings on presentation: apical four-chamber view with contrast in systole on presentation (A). Apical four-chamber view with contrast in diastole on presentation (B). Parasternal long axis view without contrast, showing a small difference in left ventricular (LV) internal diameter in systole (C) compared with diastole (D). Consistent with poor LV function on presentation (C and D). M-mode on presentation showing a small difference in LV systolic and diastolic length, suggestive of poor LV function on presentation (E). Impaired global longitudinal peak myocardial strain on presentation (F).

Figure 2 Transthoracic echocardiogram findings after L-thyroxine therapy: apical four-chamber view in systole after L-thyroxine therapy (A). Apical 4-chamber view in diastole after L-thyroxine therapy (B). Parasternal long axis view without contrast, showing a wider difference in left ventricular (LV) internal diameter in systole (C) compared with diastole (D). Suggesting improved LV function post L-thyroxine therapy (C and D). (figure 2E) M-mode after L-thyroxine therapy, showing a wider difference in LV systolic and diastolic length, consistent with improved LV function after L-thyroxine therapy (E). Normal global longitudinal peak myocardial strain after L-thyroxine therapy (F).

hypothyroidism.^{2–4} Although the merits of treating subclinical hypothyroidism have been debated, Razvi *et al*⁵ recently demonstrated improvement in cardiovascular risk factors and fatigue with L-thyroxine therapy.⁶

Our case is unique on two levels. First, to date, there are no reports of cardiomyopathy due to severe hypothyroidism among patients exposed to doxorubicin-based chemotherapy regimens. Second, our patient mounted a full recovery of systolic function with appropriate thyroid hormone therapy. This is particularly noteworthy given that patients who receive doxorubicin chemotherapy have a 3–5% lifetime risk of developing cardiomyopathy.⁷ Moreover, when due to cardiotoxic chemotherapy, cardiomyopathy represents a significant cause of long-term morbidity and mortality. Indeed, cardiac mortality in survivors of anthracycline-treated childhood cancers is more than eightfold the rate of cardiac mortality in the general population.⁷ The

degree of acuity of presentation may factor into our patient's recovery in that despite having reduced EF, this overtly hypothyroid, anthracycline-exposed patient presenting with fatigue had no evidence of cardiac remodelling, which usually leads to less reversible, dilated cardiomyopathies. It is not clear what role exposure to chemotherapy may have played in precipitating this patient's hypothyroidism, given his history of hyperthyroidism that was treated in childhood.

In summary, we presented a case of a patient with cardiomyopathy and reduced LVEF secondary to profound hypothyroidism, initially thought to be secondary to doxorubicin-induced cardiomyopathy. This case underscores the importance of screening for reversible causes of cardiomyopathy, particularly in patients with a known alternative explanation.

Contributors AJS has performed the chart review of all clinical data and literature review of all applied references. He drafted all components of the manuscript. HNP is the associate editor of the manuscript and assisted in chart review of clinical data. TO is the main editor and Director of the Cardio-oncology program at Rush University Medical Center.

Competing interests None declared.

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Learning points

- ▶ When due to cardiotoxic chemotherapy, cardiomyopathy represents a significant cause of long-term morbidity and mortality.
- ▶ Patients with a history of exposure to anthracycline chemotherapy who develop heart failure should be evaluated for reversible causes; this includes checking a thyroid-stimulating hormone to screen for hypothyroid cardiomyopathy.
- ▶ Hypothyroid cardiomyopathy is a reversible cause of heart failure that when severe can precipitate pericardial effusions and hypotension.
- ▶ Hypothyroid cardiomyopathy first manifests as impaired left ventricular systolic function and impaired myocardial strain due to increased afterload.

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