Cobalt toxicity: a preventable and treatable cause for possibly life threatening cardiomyopathy

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**ABSTRACT**

Mr BH was a 53-year-old gentleman who presented to hospital in November 2019 with decompensated heart failure, new-onset paroxysmal atrial tachycardia and increasing left hip pain. Imaging of his hip demonstrated radiographic evidence of bony changes, suggestive of an adverse reaction to metal debris (ARMD), along with a non-traumatic left peri-prosthetic neck-of-femur fracture. Clinically, he had concurrent decompensated cardiomyopathy requiring dopamine and furosemide infusions. His serum cobalt (sCo) levels were 5244nmol/L (normal<12nmol/L).

He had previous bilateral total hip arthroplasties using the Birmingham Hip Resurfacing (right side 2006, left side 2012). As part of routine metal-on-metal arthroplasty follow-up, Mr BH had sCo level checks. In 2013, these levels rose to 1981nmol/L. Although there has been no direct correlation between sCo levels and toxicity, levels above 119nmol/L are concerning. Unfortunately, Mr BH moved to a different health district and was subsequently lost to follow-up.

In 2015, Mr BH was diagnosed with dilated cardiomyopathy, presumed secondary to viral myocarditis. Despite successful chelating therapy and heart failure treatment, he passed away secondary to cobalt-toxicity induced cardiomyopathy (CTCM).

Total joint arthroplasty is a commonly performed orthopaedic procedure with the aims of relieving pain, restoring joint function and improving quality of life for patients. Last year in New Zealand, over 9,000 hip arthroplasties were performed. The Birmingham Hip Resurfacing (BHR) (Smith and Nephew, Memphis, TN) is manufactured using as-cast cobalt chrome and is classified as the world’s most successful metal-on-metal (MoM) hip resurfacing system, with over 140,000 people globally having received this implant. Prevalent use of these elements in MoM hip arthroplasty accounted for <1% of cases in 2018.

In MoM constructs, cobalt and chromium form the basis of the bearing surface, as opposed to a traditional arthroplasty construct where both femoral and/or acetabular components involve ceramic or polyethylene as part of their bearing surfaces. Revision rates of BHR occurred in 8% of cases, and the commonest cause of failure is adverse reaction to metal debris (ARMD). Despite several cases confirming cobalt-toxicity induced cardiomyopathy, there remains a paucity of high-quality research linking the cause with the effect. This makes fulfilling the Bradford Hill criteria difficult, thereby delaying the diagnosis of this potentially life threatening, yet easily preventable situation.

One in every three diagnosed cases of cardiomyopathy in general have been found to be non-ischaemic in origin. Given the established cardio-toxic effects of cobalt and its prevalent use in joint replacements, more robust systems of monitoring should be considered, especially for those at risk. Cobalt-toxicity induced cardiomyopathy is defined as both biventricular dilatation with systolic dysfunction in the presence of raised
sCo levels. It also requires normalisation of both structure and function of cardiac tissue once the insult has been removed (explanation of prosthesis or reduction of sCo levels).

Case report

Mr BH initially presented to Timaru Hospital in 2015 with progressively worsening dyspnoea and associated bilateral peripheral oedema, with preceding flu like symptoms. His history included bilateral BHR (right side 2006, left side 2012). His brain natriuretic peptide was 512ng/L (normal<40ng/L), with elevated serial troponin T (TnT) levels. A chest x-ray revealed cardiomegaly (Figure 1).

The transthoracic echocardiogram (TTE) performed showed mildly dilated ventricles with severe biventricular failure. Diagnostic coronary angiography revealed only mild diffuse atheroma. Therefore, he was diagnosed with probable viral myocarditis.

As his serial TnT levels remained elevated despite treatment with appropriate therapy, cardiac magnetic resonance imaging (cMRI) was performed to further investigate the cause of his cardiomyopathy. Unfortunately, the results were inconclusive, showing patterns of enhancement suggestive of both myocarditis and a possible infiltrative condition (Figures 2, 3 and 4).

Due to his persistently elevated serial TnT levels, a repeat cMRI was performed in 2019. This revealed progressive deterioration of his left ventricular function with ongoing features suggestive of an infiltrate condition.

The possibility of amyloidosis was raised due to the persistent nature of the findings. Myocarditis or sarcoidosis was felt to have been less likely.

As amyloidosis was felt to have been clinically unlikely, Mr BH continued with...

Figures 2, 3 and 4: cMRI showing possible delayed enhancement indicating possibility of myocarditis and sarcoidosis.
optimal medical therapy for his heart failure. He was subsequently referred for an implantable cardiac defibrillator in May 2019 due to his risk of malignant ventricular arrhythmias.

Mr BH presented back to hospital in November 2019 with an acute decompensation of his cardiomyopathy with paroxysmal atrial tachycardia. TTE demonstrated dilated cardiomyopathy with severe biventricular impairment (Figures 5 and 6). He was commenced on dopamine, furosemide and amiodarone.

Coincidentally, over the few months prior to his readmission, Mr BH had been experiencing left hip pain. Left hip imaging demonstrated features consistent with ARMD with a non-traumatic peri-prosthetic neck-of-femur fracture (Figure 7). An urgent orthopaedic review had been requested.

Repeat sCo level testing yielded a result of 5244nmol/L. Upon review of his clinical notes, we discovered that his previous sCo levels in 2013 were already elevated at 1981nmol/L. This had been requested as part of his orthopaedic follow-up historically. Unfortunately, he was lost to follow-up following his move to a different health district. Based on these results, best practice would dictate that Mr BH should undergo revision arthroplasty (rAP). However, Mr BH had become too unwell and was unfortunately deemed unfit for surgery.

Following a literature review, Mr BH was commenced on daily infusions of the chelating agent ethylenediamine-tetraacetic acid (EDTA). The improved sCo level of 1806nmol/L while on the chelating therapy (ChT) suggested that the therapy was having a positive biochemical effect.

Unfortunately, despite the biochemical improvements, Mr BH passed away while on treatment. The post-mortem review by a forensic pathologist indicated that death was due to decompensated CTCM.

Discussion
Cobalt has been used in the medical industry for years. It has been used to increase production of erythropoietin and suppress the activity of the thyroid gland. These effects commonly occur at lower blood concentrations. Therefore, CTCM can commonly be preceded by polycythaemia and hypothyroidism. However, exceptions do occur. Other contributing risk factors for CTCM include thiamine deficiency, alcoholism and a reduced protein diet. These features were not present in Mr BH.

The exact mechanism and effect of chronically elevated metal ion exposure on cellular function remains unclear. The effect of cobalt ions and their interplay with the cardiovascular system remains largely unknown. However, there have been reports of correlation between elevated sCO levels and cardio-toxic outcomes. New research around the effect of cobalt on chromosomal breaks via inhibition of DNA repair shows promising signs of shedding light on this medical enigma.

Even though the outcome of our case was unsatisfactory, key learning points should raise awareness of cobalt toxicity (CoT) and
Hopefully serve as a deterrent for future events. Timely recognition of CoT would have made rAP a potentially lifesaving venture for Mr BH. Viral myocarditis was a reasonable diagnosis for this presentation in 2015. However, background of bilateral BHR and the raised sCO levels could have raised alternative possibilities. The absence of the usual supportive features and predisposing factors of CoT would have made the diagnosis of CTCM more difficult if it was not actively considered.

The absence of a cardiac biopsy as part of the gamut of investigations performed did not help with the clarification of his presumed diagnosis. The cMRI provided an inconclusive result. These findings, together with the persistently elevated TnT levels, should have led to a cardiac biopsy.

Although endomyocardial biopsies can provide additional information, it is important to note that the findings are often non-specific and may not have altered his initial diagnosis. CoT-specific findings on histopathology may not always be present on biopsy. However, all of the findings in combination may have led to a trial of ChT and rAP, thereby possibly providing lifesaving intervention.

In light of these considerations, it would be important to note that this was not an isolated case. Looking further into CTCM, a study published in 2019 comparing 23 case reports revealed that rAP was required to extract the source of cobalt ions. Of the 23 cases, 15 had normalised cardiac function following the removal of a problematic hip joint. Six had chronic cardiac impairment. Despite receiving ChT, three of these cases still resulted in death.

ChT can be used as an adjunct or as an isolated mode of treatment if the patient is unfit for surgery. ChT can also be used before operative treatment while optimisation remains underway. Despite the increasing number of case reports being published regarding CoT and its consequences, there are still no internationally recognised and accepted guidelines on management of these patients.

Based on the literature review, there have been several studies reviewing the effects of ChT in managing elevated sCO. A study by Smith et al performed on rats investigated and compared different chelating agents, including glutathione, N-acetyl-L-cysteine, 2,3-dimercaptosuccinic acid (DMSA), diethyleneetriaminepentaacetic acid and EDTA. Their results suggest that all except DMSA were effective at reducing sCO levels. There were no formal investigations specifically on the myocardium.

A study performed by Lainiala et al in 2015 explored the effects of joint revision on serum cobalt and chromium ion levels. The explantation of the MoM prosthesis resulted in a reduction of sCO levels in all cases involving unilateral hip revisions. There

**Figure 7:** Left hip x-ray demonstrating new subluxation likely secondary to ARMD.
was also clear evidence that explanting a MoM hip arthroplasty increased the survival rate in patients with established CTCM. Therefore, the gold standard of management would seem to be rAP.

However, despite reducing whole blood levels, rAP cannot reverse tissue deposition of cobalt ions that has already occurred, such as in the myocardium. Explantation also requires the patient to be fit for surgery, which emphasises the importance of detecting CoT early, before irreversible cardiomyopathy and decompensation occurs.

The disparity between Lainiala et al’s review and our case was the mean time of presentation. Our patient was lost to follow-up despite raised sCO levels historically. In the two years it took for Mr BH to become symptomatic from his declining cardiac function, there was no formal surveillance undertaken for his hip and sCO levels.

Our centre has comprehensive systems and processes in place to monitor all patients with MoM bearing prostheses. As per the Ministry of Health, there are updated guidelines from 2012 that provide recommendations for management of patients with MoM replacements. This includes regular blood metal ion testing and imaging. In conjunction, regular TTE may be of assistance. Significant new abnormalities detected on TTE could potentially lead to further investigations with a cMRI and ultimately a cardiac biopsy.

Patients should also be educated around the potential risks involved with MoM arthroplasties. This should be highlighted and clearly acknowledged on their medical records. In our case, the realisation that Mr BH had bilateral BHR was only noted towards the final year of his life, when the records were thoroughly reviewed. This emphasises how such systems can at times leave patients with a lack of appropriate follow-up. Mechanisms must thus be in place to enable ongoing care for all patients with cobalt implants. The New Zealand Joint Registry that is already in place should be optimally used to track these patients. All surgeries should be accurately recorded and appropriately placed into categoric pools. A pool specifically for patients with cobalt implants could then be strategically used to ensure appropriate annual follow-ups are obtained. Naturally, there will always remain a risk of human error, even with accurate systems in place. Only accurate education in conjunction with knowledge around cases like Mr BH can aid in reducing such risk.

Conclusions

From the discussion above it is clear that not all MoM arthroplasties cause metal toxicity and subsequent cardiomyopathy. These procedures directly correlate with CTCM in some cases, but in many cases there is no correlation. Therefore, it is paramount that all patients who have a MoM-bearing type arthroplasty enter a surveillance programme and be monitored with a multidisciplinary approach. Annual blood tests should continue to be performed, and there should be appropriate follow-ups for any abnormal results.

High sCO concentrations should at least trigger alarm bells leading to the appropriate subsequent investigations. Delays in diagnosing CoT reduces the chance of successful interventions and outcomes. If such protocols were in place and followed, it may have been sufficient to alter and avoid the subsequent death of Mr BH.
Competing interests:
Nil.

Acknowledgements:
We would like to sincerely thank Mr BH and his family, who's strength and resilience was an inspiration to us all.

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REFERENCES