Dexamethasone suppresses long QT phenotype in patient with acute promyelocytic leukemia treated with arsenic

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Introduction

Arsenic trioxide has recently been found to improve survival and complete response when added to all-trans retinoic acid (ATRA) for the treatment of acute promyelocytic leukemia (APL). However, dose-limiting toxicity in the form of drug-induced QT prolongation limits its use in a significant percentage of patients.[1]

Preclinical models of long QT syndrome (LQTS) have demonstrated that glucocorticoids can significantly shorten the duration of the cardiac action potential.[2] However, the relevance of these findings is unclear in human populations.

Here we report the protective effects of glucocorticoid administration on QT interval in a case of APL treated with arsenic trioxide.

Case report

A 38-year-old woman who was 21 weeks gravid presented with APL. Her symptoms at presentation included headache, dyspnea, and lower-extremity edema. Her white cell count was elevated (11.9) with coagulation test results consistent with disseminated intravascular coagulation; these findings placed her in a high-risk category. Termination of the pregnancy was initially recommended, but the patient declined this course of action. Her electrocardiogram recorded at presentation showed a corrected QT interval (QTc) of 508 milliseconds, which suggested that an abnormal repolarization reserve existed even before the administration of any QT-prolonging medications (Figure 1A). No electrolyte abnormalities were noted at the time of index presentation.

The patient received high-dose ATRA on day 1, followed by induction chemotherapy with daunorubicin. Ordinarily, arsenic trioxide would have been administered at this time, but it was withheld because of the 100% risk of fetal demise. She developed retinoic acid or differentiation syndrome,[3] and she required a brief stay in the intensive care unit, for respiratory distress. Dexamethasone was administered for management of nausea and retinoic acid syndrome during induction chemotherapy, and we fortuitously observed a QTc reduction to approximately 478 milliseconds (Figure 1B). A review of her medications at this point in her hospitalization did not reveal any identifiable QT-prolonging agents. Her electrolyte levels remained within the normal range.

The patient recovered and continued ATRA therapy. Following induction chemotherapy, a bone marrow biopsy demonstrated leukemia remission with normal cytogenetic results. The patient remained pregnant, and consolidation therapy with idarubicin plus ATRA was continued from July 24, 2013, to September 19, 2013. Shortly after delivery of a full-term, healthy male neonate (Apgar scores 9/9/9), the patient began consolidation therapy with arsenic trioxide, but the first cycle was discontinued prematurely because of a QTc prolongation of approximately 581 milliseconds, which required inpatient monitoring (Figure 2A). No other QT-prolonging medications had been administered during this period, and the QT interval returned toward normal after the arsenic was discontinued (October 28 and November 4, respectively). The patient was referred to the electrophysiology (EP) department for management recommendations and facilitation of continued arsenic trioxide administration.

During the index EP visit on November 5, 2013, the patient's QTc measured approximately 481 milliseconds. Genetic testing for LQTS was ordered, and the test results eventually returned without abnormal findings. Given the benefit of arsenic trioxide to her survival, she was admitted to the hospital for QT monitoring during the first week of a second cycle of arsenic therapy. Within 2 days of starting arsenic treatment, the QTc again became markedly

KEYWORDS Arsenic; Cardio-oncology; ECG; Leukemia; Long QT syndrome

ABBREVIATIONS APL = acute promyelocytic leukemia; **ATRA** = all-trans retinoic acid; **EP** = electrophysiology; **LQTS** = long QT syndrome; **QTc** = corrected QT interval (Heart Rhythm Case Reports 2016;2:280–282)

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KEY TEACHING POINTS

- Treatment of acute promyelocytic leukemia with all-trans retinoic acid can be associated with dangerous levels of QT prolongation. The QT interval should be monitored in patients receiving this therapy.
- Glucocorticoid treatment of patients who have drug-induced QT prolongation may limit or reverse the QT prolongation.
- This case and another similar report suggest that glucocorticoid treatment in the setting of drug-induced QT prolongation may be beneficial. This observation is worthy of further investigation, although data are insufficient to make recommendations regarding patient care at this time.

prolonged, to 540 milliseconds. Starting on day 3 of hospitalization, we initiated high-dose dexamethasone (10 mg twice a day). The QTc decreased substantially within the first day of administration, to 457 milliseconds (Figure 2B). There were no changes in serum electrolyte levels over that same period.

The patient remained in the hospital for the remainder of the week for completion of the first cycle of arsenic. She was then fitted with a LifeVest (ZOLL Medical, Chelmsford, MA) and discharged to her home for the completion of outpatient administration of arsenic. The recorded QTc intervals and their correlation with arsenic and dexamethasone treatment are shown in Figure 3.

Discussion

We present a case of drug-induced LQTS with arsenic trioxide in which the patient was coincidentally treated with high-dose dexamethasone. Treatment with high-dose dexamethasone was repeatedly associated with a decrease in the QT interval that was reversible upon cessation of treatment. In this particular case, circulating cytokines due to the APL itself might be perturbing the cardiomyocyte physiology,[4] and dexamethasone might mitigate these effects. Alternatively, the induction of serum and glucocorticoid kinase has been shown to raise human ether-a-gogo–related gene (hERG) protein expression levels and might mitigate QT prolongation.[5] Thus, the relevance of this finding to other forms of drug-induced or genetic LQTS remains unknown.

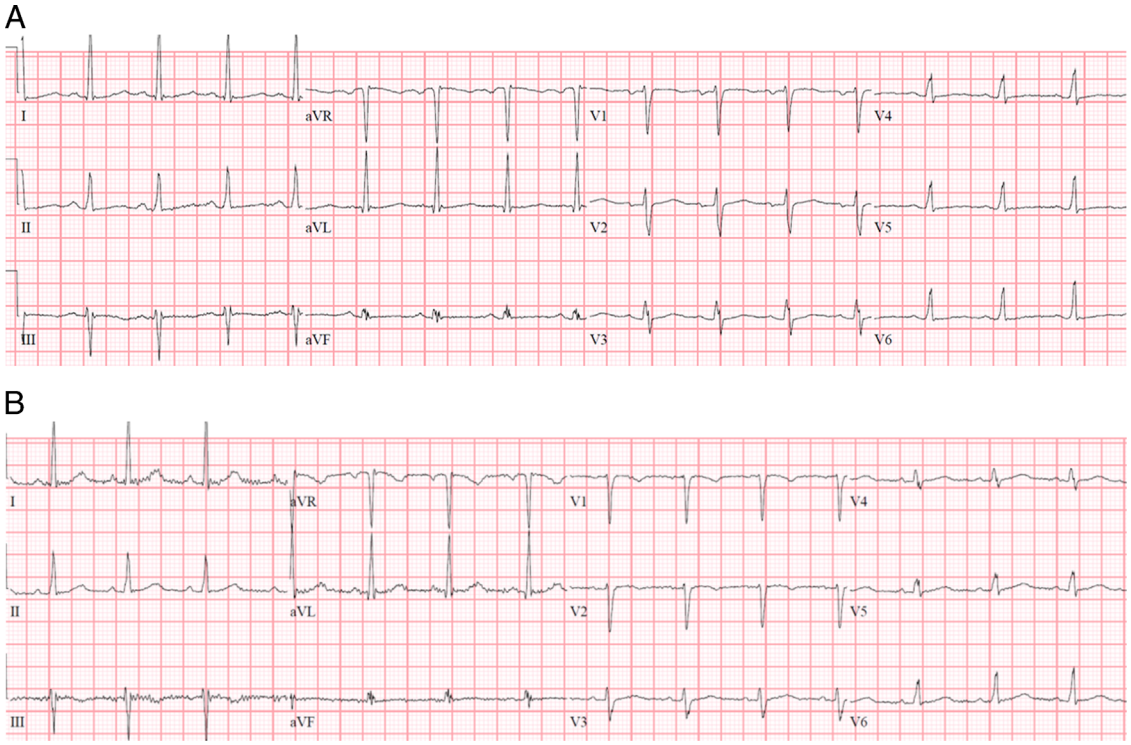

Figure 1 **A:** A baseline electrocardiogram, recorded at presentation, with QTc prolongation measuring ~508 milliseconds prior to administration of arsenic or other potential QT-prolonging agents. **B:** An electrocardiogram recorded June 29, 2013, after dexamethasone reduces QTc. Dexamethasone had been administered for nausea, and we observed QTc reduction to ~478 milliseconds.

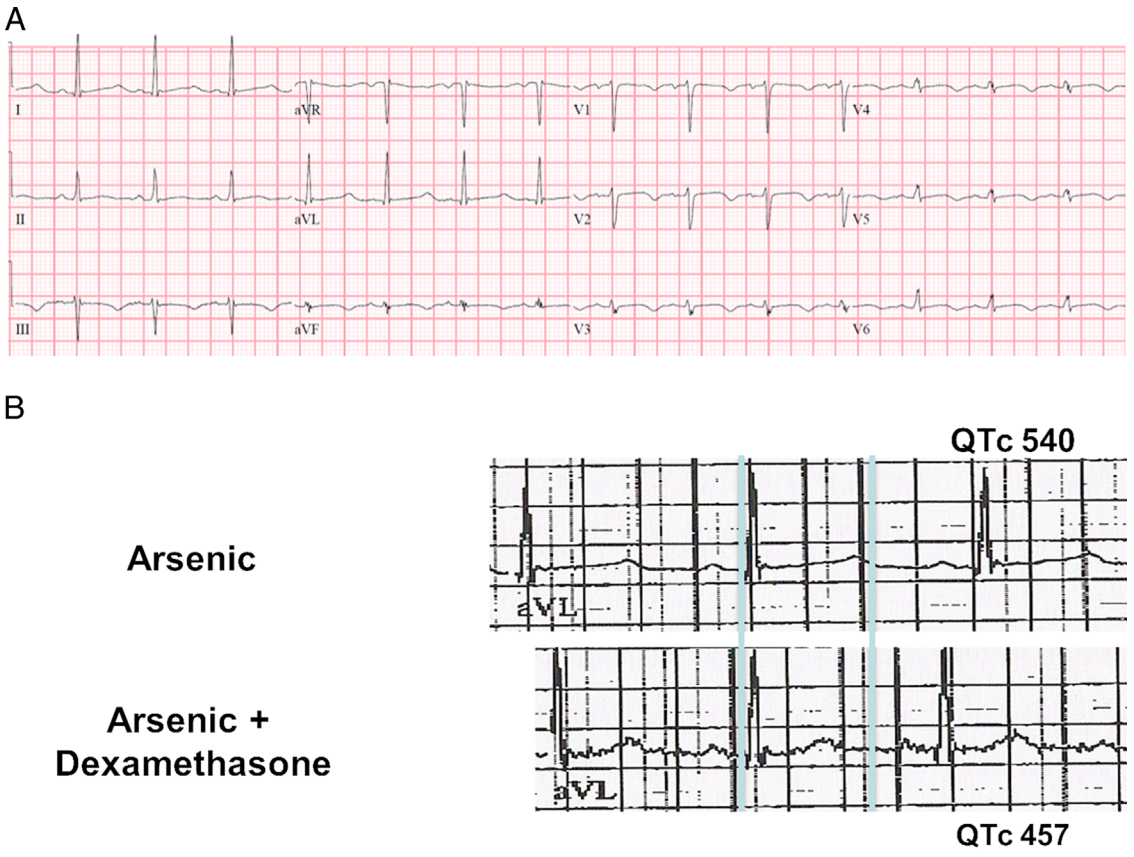

Figure 2 **A:** Marked correct QT (QTc) prolongation to 581 milliseconds during the first cycle of consolidation chemotherapy with arsenic, which resulted in therapy discontinuation and inpatient admission for monitoring. The QTc returned to baseline following the cessation of arsenic treatment. **B:** Rescue of arsenic-triggered QTc prolongation with dexamethasone. QTc measurements (blue bars indicate measurement points) during arsenic administration before and after administration of high-dose dexamethasone.

Interestingly, dexamethasone has been previously observed to shorten the ventricular action potential duration in an animal model of genetic LQTS, but its mechanism of action is unknown.[2] In addition, treatment with prednisolone has been reported to correct QT prolongation in the setting of sodium stibogluconate therapy of mucocutaneous leishmaniasis, although the glucocorticoid was not repetitively given, as it was in this case.[6] While the side effect profile of high-dose glucocorticoids would prevent long-term treatment of patients with a genetic form of LQTS, shorter-term treatment to enable life-saving therapies, such as in this case, merit further investigation.

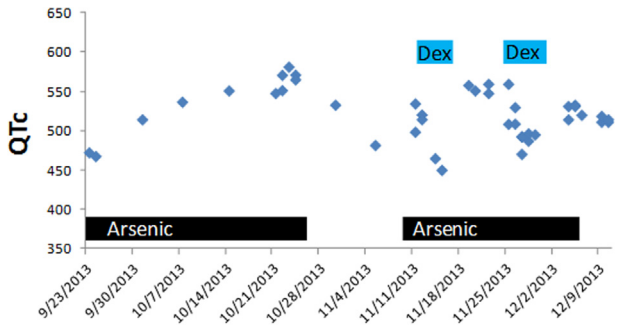

Figure 3 Corrected QT (QTc) measurements during treatment with arsenic and dexamethasone. Temporal declines in QTc correlated with cessation of arsenic therapy and also with dexamethasone treatment.

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