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Cardiotoxicity induced by Arsenic Trioxide in a patient with acute promyelocytic leukemia. A case report

Cardiotoxicidad inducida por Trióxido de Arsénico en un paciente con leucemia promielocítica aguda. Reporte de caso

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ABSTRACT

Arsenic trioxide has been used in the treatment of acute promyelocytic leukemia with good results in the hematological remission of this malignant hemopathy, but despite its effectiveness, it can bring various adverse reactions such as cardiotoxicity. The present work had as objective to describe Long QT Syndrome as an adverse reaction to the treatment with arsenic trioxide in a patient with acute promyelocytic leukemia. A case of an 81-year-old patient treated with arsenic trioxide in the Hematology Service of the Dr. Gustavo Aldereguía Lima Hospital in Cienfuegos was presented, in which Long QT Syndrome was confirmed by electrocardiography as secondary cardiotoxicity to this treatment.

RESUMEN

El trióxido de arsénico ha sido implementado en el tratamiento de la leucemia promielocítica aguda con buenos resultados en la remisión hematológica de esta hemopatía maligna, pero a pesar de su eficacia puede traer aparejadas diversas reacciones adversas como la cardiotoxicidad. El presente trabajo tuvo como objetivo describir el Síndrome del QT prolongado como reacción adversa al tratamiento con trióxido de arsénico en un paciente con leucemia promielocítica aguda. Se presentó el caso de un paciente de 81 años con tratamiento con trióxido de arsénico en el servicio de Hematología del Hospital Dr. Gustavo Aldereguía Lima de Cienfuegos en el cual se constató mediante electrocardiografía un síndrome del QT prolongado como cardiotoxicidad secundaria a dicho tratamiento.

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INTRODUCTION

Promyelocytic leukemia (PML), M3 variety of acute myeloid leukemia according to the French-American-British group classification, is undoubtedly one of the diseases that have had a change in terms of management and survival in patients. This variety of leukemia is characterized by the presence of atypical promyelocytes in blood and marrow, along with leukopenia, consumptive coagulopathy, and a peculiar immunophenotype. In the last years, different studies have been carried out which have allowed deepening the knowledge about this well-defined entity by its clinical, cytological, immunophenotypic and cytogenetic peculiarities; this variety of leukemia went from being one of the most aggressive and worse prognosis due to its high mortality to being the easiest myeloid leukemia to manage and a higher percentage of cure, achieving, in a relatively short period, the hematological and molecular remission of patients, all thanks to the introduction of molecular biology techniques and novel therapies, such as inducers of cell differentiation-maturation and apoptosis [1].

Arsenic trioxide has been approved by the Food and Drugs Administration of the United States (FDA) on September 25, 2000, for Induction of Remission and Consolidation Treatment in Patients with refractory acute promyelocytic leukemia, or with relapse to treatment. Cuba is one of the pioneer countries in the use of arsenic trioxide (ATO) as a first-line drug in the induction treatment of patients with promyelocytic leukemia at the onset of the disease [2,3].

Arsenic trioxide is commonly known to cause electrocardiographic abnormalities, producing QT prolongation in 50 % of patients. Other side effects include sinus tachycardia, nonspecific changes in the ST-T and torsade de pointes [4].

Long QT Syndrome is a set of rare entities that are manifested on the electrocardiogram (ECG) by prolongation of the QT interval (men> 450 msec and women> 470 msec) and predisposition to polymorphic ventricular tachycardia. The incidence is 1: 5 000 or 10 000 and is responsible for about 3 000 deaths per year in the United States in children and young adults [5].

In the national bibliography consulted, the authors of this investigation couldn't find any information about the incidence of this morbidity in Cuba.

With the advent of new cancer treatments, day by day is more common the appearance of cardiotoxicity produced by chemotherapy, which if is not detected and corrected in time can lead to dire consequences to the life of the patient. The limited scientific documentation about the Long QT Syndrome as a rare type of cardiotoxicity motivated the realization of the present work, whose objective is to describe the Long QT Syndrome as an adverse reaction to the treatment with arsenic trioxide in a patient with acute promyelocytic leukemia.

CASE REPORT

An 81-year-old black male patient of rural origin with a past medical history of rectal tumor and inguinal hernia about 10 years ago for which he underwent surgical treatment, and hypertension about 5 years ago with regular treatment with captopril (25 mg) 3 tabs/day and hydrochlorothiazide (25mg) 1 tab/day. He came to the "Dr. Gustavo Aldereguía Lima" Hospital in Cienfuegos on April 2018 complaining of decay and dizziness of six months of evolution. For that reason, some complementary exams were indicated, those reported anemia and thrombocytopenia, and the patient was transfused on two occasions for presenting very marked anemia.

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A medullogram was performed and it informed the presence of blast cells and doctors diagnosed an acute promyelocytic-type myeloid leukemia and the patient received initial treatment with the COAP scheme (cyclophosphamide, vincristine, cytosine arabinoside and prednisone) and cytosar in low doses completing four cycles. Unfortunately, he did not obtain any improvement and it was decided to change the treatment to arsenic trioxide (ATO) and a microdose of ARA-C. The first cycle of ATO was administered on 8/17/18, the same day in the morning an ECG was performed and it presented no alterations.

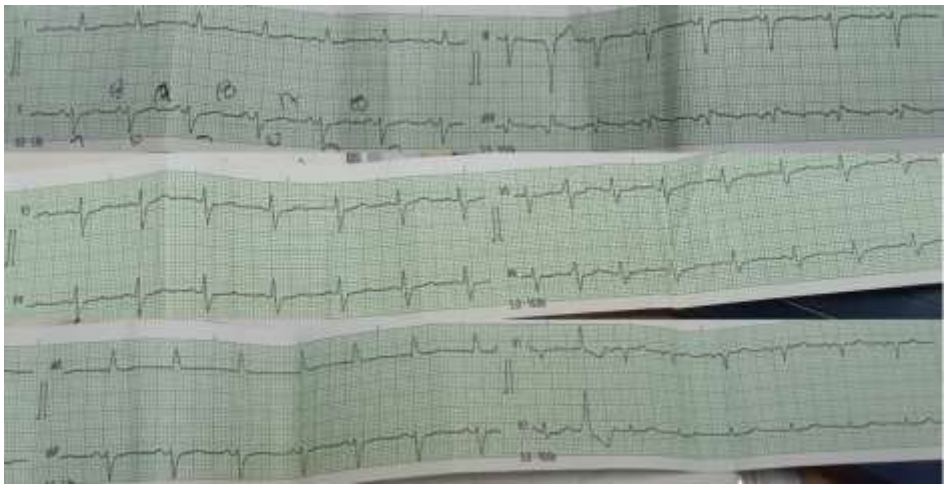
Subsequently, on 8/22/18 an ECG was repeated (see figure 1) where doctors noticed a slight prolongation of QTc interval (455 msec). The day the second ATO cycle was supposed to start (9/10/18) a new ECG was performed (see figure 2) and the QTc interval was even longer (471 msec); therefore, it was concluded that the patient suffered from chemotherapy-induced cardiotoxicity and consequently doctors took as behavior to suspend the treatment with ATO and to discharge the patient with ambulatory cytosar.

Later, on December 9th, 2019, he entered again to reevaluate the possibility of continuing treatment with arsenic, with this purpose doctors performed an ECG in which the QTc was 400 msec, so it was decided to use the arsenic. Three days later, the ECG was repeated (see figure 3) in which was observed a long QTc (490 msec) and ventricular extrasystoles, accordingly to this, doctors took conduct of suspending the ATO again for being cardiotoxic and discharge the patient with ambulatory cytosar. As further management for his cardiotoxicity, the patient was periodically monitored by electrocardiography, and the administration of other QT-prolonging drugs was avoided.

During the evolution of his disease, he underwent several complementary examinations:

Echocardiogram (4/25/18): deficient window, left ventricle with a slight tendency to remodeling and hypokinetic. Right ventricle approximately 57 mm, ejection fraction of the left ventricle of 50%. Mitral valve with decreased opening by calcification of the leaflets. No effusion or intracardiac masses. Normal right cavities. Left atrium 36 mm. Type I diastolic dysfunction.

Figure 1: ECG of the patient where QTc of 455 msec is observed



Source: Patient's medical history

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Table 1: Blood counts and blood chemistry revealing anemia during the patient's illness. In addition to neutropenia and thrombocytopenia

	COAP 1 (3/5/18)	COAP 2 (30/5/18)	COAP 3 (22/6/18)	COAP 4 (16/7/18)	TOA 1 (17/8/18	TOA 2 (10/9/18)
Hemoglobin	85 g/L	94 g/L	101 g/L	124 g/L	102 g/L	78 g/L
Hematócrit	26%	29%	30%	38%	31%	25%
Leukocytes	8.4 x 10^9/L	6.0 x 10^9/L	4.2 x 10^9/L	3.6 x 10^9/L	4.6 x 10^9/L	3.8 x 10^9/L
Stab	0.00	0.02	0.00	0.02	0.00	0.00
Segmented	0.64	0.77	0.44	0.41	0.79	0.62
Eosinophils	0.07	0.02	0.00	0.01	0.00	0.00
Monocytes	0.00	0.03	0.04	0.02	0.00	0.20
Lymphocytes	0.29	0.16	0.52	0.54	0.29	0.36
Platelet count	160 x 10^9/L	154 x 10^9/L	180 x 10^9/L	300 x 10^9/L	150 x 10^9/L	100 x 10^9/L
Blood glucose	5.71 mmol/L	6.55 mmol/L	5.89 mmol/L	5.8 mmol/L	5.63 mmol/L	6.62 mmol/L
Creatinine	81 µmol/L	82 µmol/L	89 µmol/L	87 µmol/L	90 µmol/L	85 µmol/L
Uric acid	459 µmol/L	437 µmol/L	441 µmol/L	445 µmol/L	253 µmol/L	N/R
GPT	14 UI/L	20 UI/L	17 UI/L	16 UI/L	35 UI/L	21 UI/L
GOT	13 UI/L	16 UI/L	15 UI/L	16 UI/L	38 UI/L	19 UI/L

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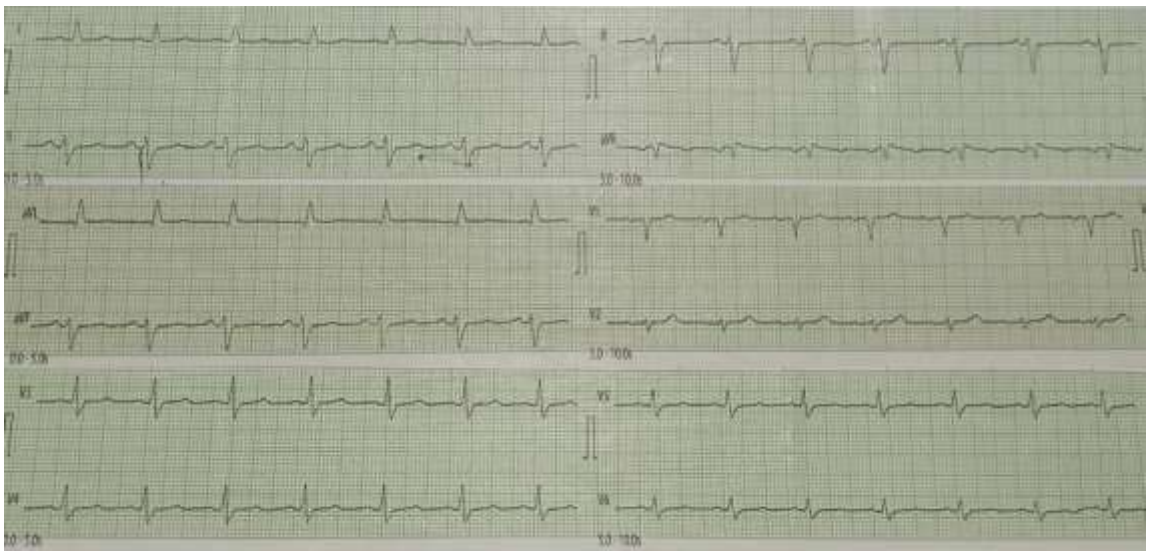
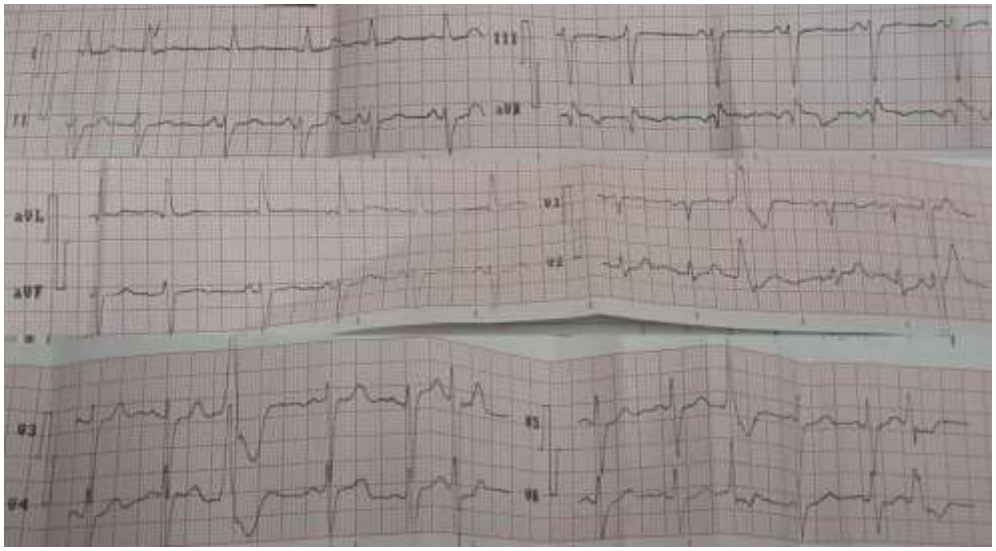
LDH	N/R	N/R	N/R	N/R	N/R	306 UI/L
GGT	13 UI/L	47 UI/L	28 UI/L	33 UI/L	42 UI/L	17 UI/L
ALP	229 UI/L	N/R	245 UI/L	336 UI/L	270 UI/L	255 UI/L

Figure 2: ECG of the patient showing QTc of 471 msec



Source: Patient's medical history

Figure 3: ECG of the patient showing QTc of 490 msec and ventricular extrasystoles



Source: Patient's medical history

DISCUSSION

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The QT interval is the electrical systole of the ventricles and extends from the onset of the QRS complex until the end of the T wave. Its duration is influenced by the heart rate, age and sex. Its "abnormal" prolongation means that there is delayed repolarization; it may increase susceptibility to sudden death (Long QT Syndrome). The normal duration of corrected QT (QTc) is up to 470 msec for women and 450 msec for men [6].

According to Hernández M.[7] its prolongation may predispose to the appearance of a severe polymorphic ventricular tachycardia called torsion of tips (TdP or torsade de pointes) manifesting as syncope, dizziness, or palpitations; and, even though it usually resolves spontaneously, it can trigger ventricular fibrillation and sudden death. This is not the case of the patient because in his case the existence of long QT syndrome was only demonstrated by electrocardiography and it didn't have clinical manifestations attributable to it.

In clinical studies of the Spanish Agency for Medicines and Health Studies, in relapsed/refractory cases, 40 % of patients treated with trioxide of arsenic experienced at least one prolongation of the corrected QT interval (QTc) longer than 500 msec. A prolongation of the QTc interval was observed within one and five weeks after arsenic trioxide infusion, returning to the normality in eight weeks approximately [8]. This is related to the case of the patient because it presented at the time that the second cycle of ATO was due to be administered and it returned to normality after the ATO was suspended.

Patients should be careful taking concomitant medicinal products that may increase the QT interval (for example some antiarrhythmics or thioridazine) or others which may lead to electrolyte disorders (diuretics or amphotericin B) [9]. The patient in addition to the ATO, was taking hydrochlorothiazide (diuretic) because of his hypertension but doctors determined to maintain that treatment in a low dose. There are several meassures that should be taken into account in order to achieve a global and interdisciplinary approach to patients under chemotherapy treatment and to facilitate an adequate evolution; for instance: cardiovascular evaluation, risk analysis, prevention and mitigation of the cardiac injury and monitoring of the heart function during and after therapy [10]. In the case of the patient was monitored by Cardiologists and Hematologists and followed by electrocardiograms.

CONCLUSIONS:

Treatment with arsenic trioxide is a novel practice that has revolutionized the prognosis and survival of patients suffering from acute promyelocytic leukemia that relapses or does not respond adequately to the usual treatment. Parallel to these auspicious results, cardiotoxicity appears as a major adverse reaction that should always be taken into account for the correct management and comprehensive care of these patients.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORITY STATEMENT:

RACR: Conception and design of the study. He participated in the conception, analysis and discussion of the information, in the revision, correction and approval of the manuscript. **MCAC:** He was in charge of the writing of the manuscript, and the revision, correction and approval of the manuscript. **LPB:** Was in charge of downloading the bibliographic references, and in the revision, correction and approval of the manuscript. **MMCZ:** Participated in the review of the final manuscript.

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