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Syncope-Related Sinus Pause Secondary to the Use of Thalidomide in an Oncological Patient

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Abstract

Introduction: Advances in oncological therapy have improved the survival rates of this population. The cardiovascular risk factors and cardiotoxicity control remains challenging, since drug interactions may result in significant clinical events.

Methods: This study describes a cardiotoxic event caused by syncope-related sinus pause, exacerbated or resulting from the use of thalidomide in a patient during multiple myeloma treatment.

Results/Discussion: A 63-year-old male submitted to VAD (vincristine, doxorubicin and dexamethasone) chemotherapy for multiple myeloma. After six months, the patient underwent a Bone Marrow Transplant (BMT), first with thalidomide, evolving with successive syncopal episodes (Stokes-Adams syndrome), one of which resulted in traumatic brain injury, with a fracture in the left temporoparietal region. A 24-h Holter showed 2 pause episodes of more than 2 sec, the longest being 18.5 sec, not associated with symptoms. It is known that patients submitted to chemotherapy are at risk of developing cardiotoxicity. Preventive measures should be part of clinical management, in order to prevent ventricular damage and the occurrence of other phenomena.

Conclusion: The use of thalidomide requires monitoring bradyarrhythmia's and syncope. Medication with greater tolerability, such as lenalidomide, should be increasingly prescribed, thereby avoiding undesirable clinical situations that may directly affect patient morbidity and mortality.

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Introduction

The demographic and epidemiological transition process that occurred in Brazil and the world in the last century changed the profile of the most prevalent diseases. Increased life expectancy and improvement in certain aspects of the health-disease process led to a reduction in infectious and parasitic diseases, with a rise in the incidence of neoplastic diseases. Thus, neoplasm's that accounted for around 3% of overall deaths in 1930, increased proportionally to 12% in the mid-1980s [1].

There have been important advances in the area of medicine, with new drugs and treatments to manage these diseases. On the other hand, new drug interactions may result in a significant clinical event in the follow-up of this population [2]. This can be particularly relevant given the need to control cardiovascular comorbidities prevalent in survivors.

One of the concerns with the use of antineoplastic agents is the potential for cardiotoxicity. This clinical entity is defined by confirmation of new clinical cardiovascular alterations during or after antineoplastic treatment and/or change in biomarkers and/or cardiac imaging tests, provided other etiologies have been excluded [3,4].

Multiple myeloma, a malignant disease of the hematopoietic system, was one of the neoplasm's whose natural history was modified. Despite still being incurable, the therapeutic arsenal has been broadened.

The aim of this study was to describe a cardiotoxic event caused by syncope-related sinus pause, exacerbated or caused by the use of thalidomide in a patient being treated for multiple myeloma.

Case Presentation

A 63-year-old male was referred to the cardio-oncology outpatient facility due to hypertension after the onset of VAD (vincristine, doxorubicin and dexamethasone) chemotherapy to treat multiple myeloma. There were no cardiovascular symptoms at that time. The patient was using 10 mg/d of amlodipine and 50 mg/d of metoprolol tartrate. Physical examination showed a good overall state, pallor, FC I with BP= 44 mmHg × 86 mmHg, HR= 84 bpm, and RR=22 ipm. CMR

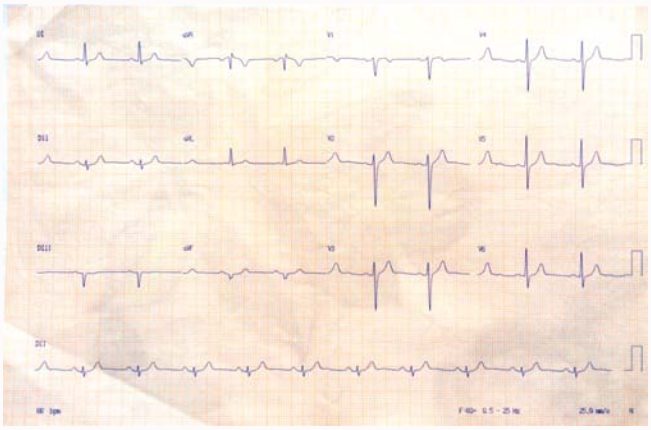

Figure 1: Electrocardiogram at patient admission.

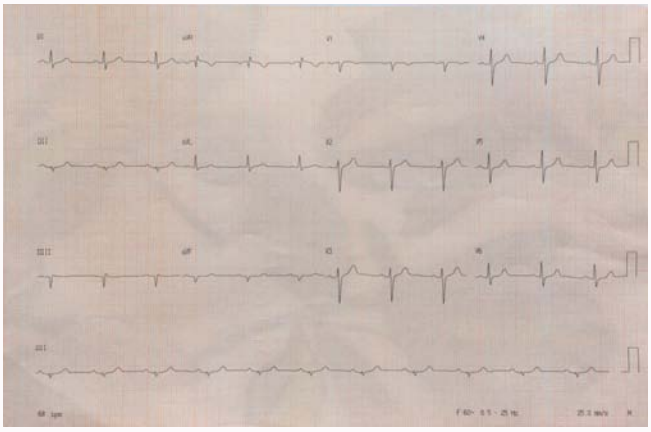

Figure 2: ECG image obtained after BMT and syncope.

at 3T, with 4S, A2 hyperphonesis and mitral regurgitation murmur (+/6+). No systemic or pulmonary congestion or other disorders were detected.

Complementary examinations at follow-up showed an electrocardiogram with sinus rhythm, left-axis deviation, electrically inactive lower wall area, and QTc of 426 msec (Figure 1). Transthoracic echocardiogram revealed grade I diastolic dysfunction, with preserved systolic function (LVEF=69%), and no change in segmental contraction. Due to the high risk of cardiotoxicity, the anti-hypertensives were replaced by 20 mg/d of enalapril and 6.25 mg/d of carvedilol. There was good tolerance to increasing doses of carvedilol up to 50 mg/day.

After six months, the patient was submitted to a Bone Marrow Transplant (BMT), with thalidomide as part of the BMT hematology protocol, evolving with successive syncopal episodes (Stokes-Adams syndrome), one associated with traumatic brain injury and a fracture in the left temporoparietal region. At this time, the physical examination was similar to that of the first consultation, with controlled blood pressure, no postural hypotension or other disorders, and CMR with 4S. The electrocardiogram exhibited the same pattern as those previously obtained (Figure 2).

The 24-h Holter showed 2 pause episodes of more than 2 sec, the longest being 18.5 sec, not associated with any symptoms (Figure 3). After joint assessment with an Arrhythmologist, the following diagnostic hypotheses were considered: Thalidomide-induced bradycardia, ventricular arrhythmias caused by cardiotoxicity due to the previous use of doxorubicin or vasovagal syncope resulting from a change in the antihypertensive scheme. The use of 25 mcg/d of fludrocortisone was prescribed, associated with non-pharmacological measures, and the beta blocker was discontinued, while complementary diagnosis assessment progressed. Syncopal episodes persisted with similar characteristics to those previously observed.

The electrophysiological study to assess sinus node dysfunction was normal, as was cardiac catheterization, which demonstrated only epicardial coronaries with irregularities. The tilt test was negative.

Thyroid function and electrolyte doses remained normal throughout follow-up. Due to the persistent syncopal episodes and the impossibility of suspending thalidomide, a definitive atrial-ventricular pacemaker was implanted, with successful episode resolution.

Discussion

Syncope occurred in the patient due to a confluence of factors, including base pathology, since cancer leads to a proinflammatory state that may culminate in fibrosis and altered cardiac physiology, the side effects of his medication. The use of thalidomide seems to be the main factor for the origin of syncope.

Thalidomide, an antineoplastic drug, is part of the therapeutic scheme for multiple myeloma. Its most important cardiotoxicity-related side effects are thromboembolic phenomena and arrhythmias, mainly bradyarrhythmia's [5]. Some studies found that thalidomide could induce mild bradycardia in up to 55% of patients, irrespective of an association with corticosteroids [6,7]. The most severe bradycardia symptoms occur in only 1% to 3% of cases [7]. Numerous mechanisms are involved in the hemodynamic determination of cardiac arrhythmias, such as hypotension and pulmonary hypertension [7,8].

Fahdi et al. [9] reported topics that deserve attention. More than 90 patients with multiple myeloma treated with thalidomide were compared with the control group. Their concomitant use with negative chronotropic drugs, such as adrenergic beta calcium channel blockers, and antiarrhythmic drugs showed no statistically significant difference in relation to the occurrence of bradyarrhythmia's in the study patients [9,10]. However, along with doxorubicin and cyclophosphamide, these drugs are part of the group that pose a risk for the occurrence of bradycardia [11]. An important factor that seems to be associated with greater sinus bradycardia occurrence is the existence of concomitant hypothyroidism, which should be closely monitored [7]. In the patient in question, all thyroid hormone contents were normal.

Electrocardiographically, bradycardia is expressed with no change in intracardiac conduction intervals, such as the PR, QRS and QT interval. The physiopathological mechanism remains unknown [7]. Fahdi et al. [9] suggested that the basis for the occurrence of this event is the imbalance caused by thalidomide in the sympathetic and parasympathetic nervous systems. Thalidomide inhibits TNF alpha expression and activity, leading to complete inhibition of the dorsal motor neuron in the vagus nerve nucleus, resulting in parasympathetic hyperactivity and culminating in sinus bradycardia and other conduction disorders, such as third-degree atrioventricular block [7,9,12].

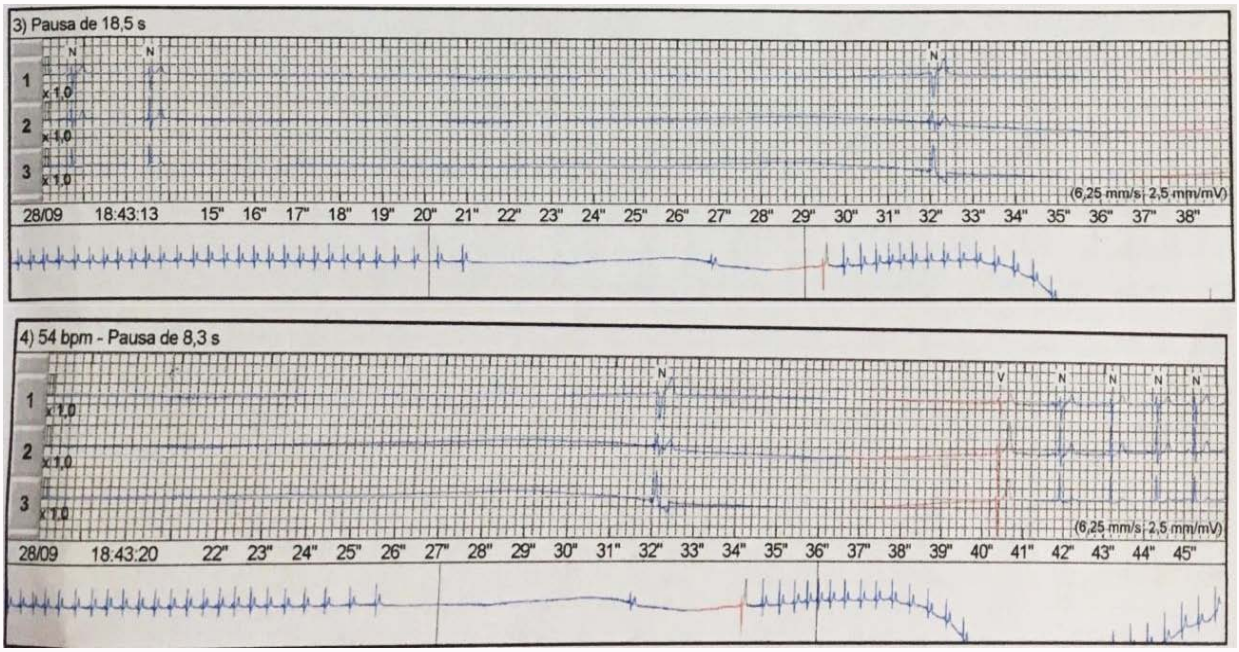

Figure 3: 24-hour graph showing important sinus pauses, the longest being 18.5 seconds.

It was later suggested that the harmful effect of this chemotherapy drug is dose dependent, as reported by Tamargo et al. [7], such that in patients where it could not be reduced or suspended, when severe bradycardia occurs, the typical therapeutic alternative is implanting a definitive pacemaker [7,9]. This device has increased in patients exhibiting syncopal episodes. Thangaraju et al. [13] reported the occurrence of sinus bradycardia in young patients being treated for erythema nodosum leprosum, and no association with other drugs. This resulted in regression and return to basal heart rate after the drug was suspended, demonstrating that the effects are associated with higher serum concentration of the drug and suggesting the reversibility of the effects of thalidomide in sinus node function [7,9,13-15].

In a study of patients diagnosed with stage 1 multiple myeloma, Rajkumar et al. [16] found that at an average of 400 mg/day of thalidomide (varying from 200 mg/day to 800 mg/day), around 26% of the patients exhibited bradycardia, showing an association with a lower heart rate. The same phenomenon was observed by Menghui [17], where sinus bradycardia was one of the most important side effects of thalidomide in terms of morbidity in the treatment of Crohn's disease, reinforcing the need to monitor cardiotoxicity.

There are now drugs with a more tolerable cardiovascular toxicity profile, including second-generation immune modulators such as lenalidomide, a thalidomide analog [18]. However, this drug is not available in the Brazilian public health system, since it was not included in the National List of Essential Drugs (RENAME), last updated in 2022 [19].

It is known that patients submitted to chemotherapy are at risk of developing cardiotoxicity. Preventive measures should be part of clinical management, in order to prevent ventricular dysfunction and other phenomena. Although not statistically significant, according to the latest Brazilian Cardio-Oncology Guidelines, the use of Angiotensin Converting Enzyme (ACE) inhibitors and prophylactic beta blockers is indicated, irrespective of symptomatic or asymptomatic cardiac injury [3]. In the largest randomized clinical trial conducted to prevent cardiotoxicity using adrenergic beta blockers, specifically carvedilol, Avila et al. [20] found no difference between the control group and placebo in relation to left ventricular ejection fraction and placebo, since there was a decline in troponin levels and diastolic dysfunction in the carvedilol group. It is important to note that in addition to their side effects, these drugs may interact with the chemotherapy drugs themselves.

Conclusion

The use of thalidomide requires careful monitoring of bradyarrhythmia's and syncope, in addition to other cardiotoxicities. Drugs such as lenalidomide exhibit better tolerability and less interaction with therapies to control comorbidities and reduce cardiotoxicity. As such, they should be preferred to lower the risk of undesirable clinical situations and increased morbidity and mortality in this population.

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