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Extra-Pulmonary Tuberculosis in the Uterine Cervix: A Case Report

Charles Lukanga Kimera[1*], Fredrick Sinyinza[2], Linda Ndesipandula Lukolo[3]

[1]Department of Maternal & Child Health, Obstetrics & Gynaecology, School of Medicine, University of Namibia, Windhoek, Namibia
[2]Department of Maternal & Child Health, Paediatrics, School of Medicine, University of Namibia, Windhoek, Namibia
[3]Department of Community and Family Medicine, School of Medicine, University of Namibia, Windhoek, Namibia
Email: *kimerassuuna@gmail.com, *lkimera@unam.na

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Abstract

Tuberculosis of the uterine cervix is grouped under genital tuberculosis. Other sites for genital tuberculosis include the Fallopian tubes and the endometrium. Genital tuberculosis and other types of tuberculosis outside the lungs are referred to as extra-pulmonary tuberculosis (EPTB). Genital tuberculosis presents with unspecific symptoms and signs; and because of this, most often, the diagnosis is made incidentally during investigations for other conditions that present with similar clinical pictures. Therefore, misdiagnosis and wrong treatment are not uncommon. We present a case of tuberculosis of the uterine cervix which was incidentally diagnosed when the patient was being investigated for cervical cancer, and successfully treated with a 6-months rifampicin regimen, 2RHZE/4HRE. Health providers have a duty to highly suspect tuberculosis of the cervix among women who present with abnormal vaginal discharge, abnormal vaginal bleeding and post-coital bleeding especially in countries where HIV and TB are endemic. If properly diagnosed and correctly treated, tuberculosis of the uterine cervix is curable.

Keywords

Tuberculosis, Extra-Pulmonary Tuberculosis, Genital Tuberculosis, Post-Coital Bleeding, Cervical Tuberculosis

1. Introduction

Tuberculosis is an ancient disease that has been a major cause of suffering and death for many years. TB has been the leading cause of death among infectious diseases. Successful antibiotic treatment only became possible in 1948. In hu-

mans, tuberculosis is caused by the bacillus *Mycobacterium tuberculosis*. It mainly affects the lungs, although it can affect any organ in the body (extrapulmonary TB). The tubercle bacilli were first described by Robert Koch in 1882.

The prevalence of tuberculosis tends to be higher among HIV-infected individuals. According to the WHO global TB report of 2018, there were 10 million new TB cases notified in 2017 worldwide, of which 9% were co-infected with HIV.

Tuberculosis (TB) can either be pulmonary (PTB), extrapulmonary (EPTB) or both. A patient with both pulmonary and EPTB is classified as a case of PTB. Pulmonary TB is the most common form of the disease, and is of public health importance due to its infectiousness. EPTB refers to TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges or genitourinary system). EPTB is more common in patients who are infected with HIV, with a prevalence of about 20% [1] [2].

Whereas chest radiography and laboratory tests are used to diagnose pulmonary TB, a normal chest X-Ray and/or negative laboratory tests do not exclude EPTB, especially in patients who are HIV positive. Therefore, whenever screening for TB in PLHIV, the screening should include all EPTB sites.

Few cases of cervical Tuberculosis have been documented worldwide. The commonest presenting complaints for cervical tuberculosis are persistent offensive discharge, abnormal vaginal bleeding, malaise and postcoital bleeding. Speculum examination often reveals cervical lesions which may appear as either exophytic, ulcerative or endocervical polyploids. These lesions are often mistaken for cancer of the cervix [3]. Patients with Cervical TB do not often present with the clinical picture of pulmonary TB such as cough, unexplained fever or night sweats [4].

A case of cervical tuberculosis in a woman who presented with post-coital bleeding and irregular menstrual bleeding is being presented.

2. Case Summary

A 23-year-old nulliparous woman presented to a gynaecology clinic with post-coital bleeding and irregular menstrual periods. Review of her medical and surgical history revealed that she was on highly active antiretroviral therapy (HAART) treatment since her childhood and she was adherent to treatment; she had been treated for abdominal pain in the surgical department where they performed laparoscopy and she was informed that she had peritoneal adhesions but she got no further treatment following surgery. She otherwise denied history of cough, fever and night sweats. Examination revealed a young lady in good physical condition. Significant findings were on speculum examination which showed a lesion on the cervix that easily bled on contact (**Figure 1**).

Because of the postcoital bleeding, the lesion on the cervix and HIV status, we made a provisional diagnosis of cancer of the cervix. A biopsy was taken from the cervix to rule out cancer of the cervix. The results showed multiple caseating epithelioid granulomas of varying size with multinucleated cells in the stroma suggestive of tuberculosis (**Figure 2**). There were no cancer cells, hence cancer of

Figure 1. Photograph of the cervix at speculum examination.

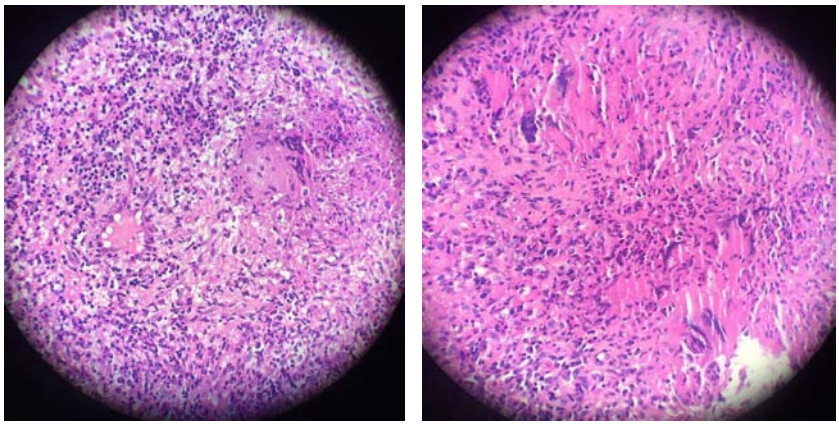

Figure 2. Histological images showing multiple epithelioid granulomas with multinucleated cell in the stroma.

the cervix was ruled out. The laboratory further performed the Ziehl Neelsen (ZN) test on the specimen and results were positive for alcohol acid fast bacilli (AAFB). A diagnosis of TB of uterine cervix was then made. Results of full blood count (FBC) and differential count were normal apart from the slightly elevated mean platelet volume (MPV). This was considered to be of little significance.

The patient was put on traditional standard treatment regimen for tuberculosis. Follow-up for treatment refill and review of symptoms and signs was done monthly. After six months she had completely recovered. Her menses had normalised and she no longer had post-coital bleeding.

3. Discussion

In humans, tuberculosis (TB) has been known for a long period of time, probably 3 million years but the organism that causes TB, *Mycobacterium tuberculosis*, was only described in 1882 by Robert Koch after it had killed a number of people both in United States of America and United Kingdom [5] [6]. Since that

time a lot has been learnt about transmission of the organism, vaccination against TB and its treatment. However, despite the knowledge and the availability of vaccination and treatment for the disease, TB is still a common problem among many populations of the world.

Tuberculosis commonly (77%) affects the respiratory (pulmonary) system causing cough as the most common symptom. Other associated symptoms include night sweats, fever weight loss, lymphadenopathy, etc. Tuberculosis affects mainly individuals with lowered immunity, and with the epidemic of human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS), the disease it causes, tuberculosis also became more rampant among populations. According to the WHO global TB report of 2018, there were 10 million new TB cases notified in 2017 worldwide, of which 9% where co-infected with HIV [7]. Our index case was a young lady with HIV, which was vertically transmitted, and was on a life-long treatment with antiretroviral drugs. This could have increased her chances of suffering from TB.

Extra pulmonary TB is found in sites like skeletal, plural space, abdomen, Fallopian tubes, endometrium and cervix. Most extrapulmonary TB is difficult to diagnosed from clinical symptoms, suggesting a high likelihood of diagnostic delays and misdiagnosis, hence wrong treatment [8].

Tuberculosis of the uterine cervix is rare, accounting for 0.1% - 0.65% of all cases of tuberculosis (TB) and 5% - 24% of genal tract TB [9]. It usually presents with abnormal vaginal discharge, post-coital bleeding and intermenstrual bleeding. These symptoms and/or signs are commonly found in patients with cervical cancer. This clinical presentation, therefore, makes service providers think about carcinoma of the cervix rather than uterine cervix tuberculosis. The case discussed here was also provisionally diagnosed as cancer of the cervix, however investigations ruled it out. It is therefore important to have a high index of suspicion of cervical TB when dealing with young women with such clinical presentation especially if there is history of contact with a smear-positive pulmonary TB patient, past history of TB infection or if they are living with HIV and are of low socio-economic status [10].

This patient had initially complained of abdominal pain and at laparotomy adhesions were found but these were not taken seriously. It is likely that by this time she had pelvic tuberculosis and a biopsy, at laparoscopy, would have been helpful at making a diagnosis. In the gynaecology clinic, however, a biopsy was taken from a suspicious lesion on the cervix to rule out cancer of the cervix. Results were negative for cancer of the cervix but positive for tuberculosis.

The patient was put on the traditional standard treatment regimen as par WHO 2010 treatment guidelines for tuberculosis [11]. After six months she had completely recovered, her menses had normalised and she no longer had post-coital bleeding. Notably this is the same treatment regimen given for the management of tuberculosis in any other part of the body including CNS tuberculosis.

4. Conclusion

Because of the similarity of its clinical presentation to that of cervical cancer, tuberculosis of uterine cervix is commonly misdiagnosed as cancer of the cervix. Health providers, therefore, should have a high index of suspicion among women who present with abnormal vaginal discharge, abnormal vaginal bleeding and post-coital bleeding especially in countries where HIV and TB are endemic. Punch biopsies should be taken from suspicious lesions on the uterine cervix for histological examination to make the definitive diagnosis. If correctly diagnosed and appropriately treated tuberculosis of the uterine cervix is curable, yet without proper treatment, it can lead to a multitude of complications and death.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Slow and Steady: The Cautious Use of Neuroleptics in a Patient with Andersen-Tawil Syndrome

Fahad Alkhalfan[1], Bharadwaj Adithya-Sateesh[2], Girma M. Ayele[3], Merve Otles[2], Rediet T. Atalay[3], Miriam Michael[1,3]

[1]Department of Internal Medicine, University of Maryland, Baltimore, USA
[2]Department of Internal Medicine, College of Medicine, American University of Antigua, Antigua, Antigua and Barbuda
[3]Department of Internal Medicine, Howard University Hospital, Washington DC, USA
Email: miriambmichael@gmail.com

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Abstract

Long QT syndrome (LQT) is a disease of cardiac repolarization caused by alterations in the transmembrane potassium and sodium currents. This results in prolongation of the QT interval on electrocardiography (EKG) and can result in torsade de pointes and sudden cardiac death. We present a case of a patient who has Anderson Tawil syndrome; a congenital long QT syndrome, with a history of cardiac arrhythmias who developed acute paranoid schizophrenia that was refractory to treatment with non-QT-prolonging drugs and required institution of neuroleptics to control her psychiatric symptoms.

Keywords

Long Q-T Schizophrenia, Neuroleptic, Anderson Tawil Syndrome, Congenital Long QT Syndrome

1. Introduction

Congenital long QT syndrome (LQTS) refers to a group of heterogeneous cardiac electrophysiologic disorders that are characterized by abnormal ion function [1] [2]. This can lead to changes, including QT prolongation and T-wave abnormalities which are detected on an electrocardiogram (ECG). It is diagnosed using clinical presentation, family history, and typical ECG characteristics [1]. While most patients are asymptomatic and diagnosed incidentally on ECG, patients can present with syncope, dizziness or palpitations [3] [4]. The syncope here typically occurs during exercise and high emotions and is usually abrupt and without warning, differentiating it from orthostatic or vasovagal syndrome.

Additionally, sudden death can also occur due to the development of Torsades de Pointes [1].

The cornerstone of managing patients with LQTS is avoiding QT-prolonging medications that can decrease repolarization reserve and subsequently lead to an increased risk of malignant and potentially fatal arrhythmias [5]. However, there may be situations where these medications may be unavoidable. We describe the case of a patient with Andersen-Tawil syndrome who was admitted to the medical service for careful titration of her antipsychotic medications.

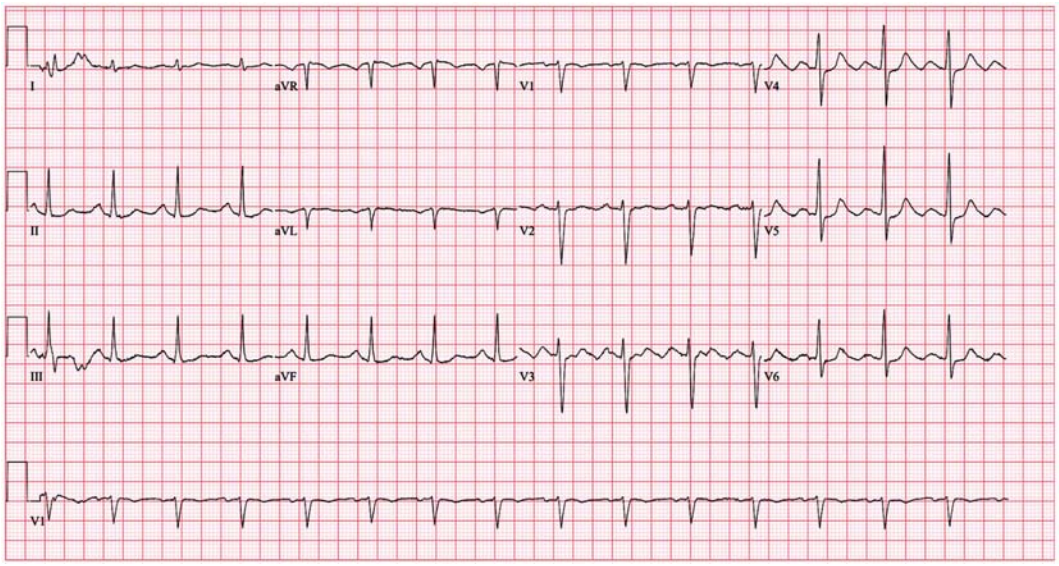
2. Case Presentation

A 37-year-old female with a past medical history of Long QT syndrome with bidirectional PVCs consistent with Andersen-Tawil syndrome and schizophrenia was admitted to the intermediate medical care unit from the psychiatry unit to initiate antipsychotic pharmacotherapy while closely monitoring her cardiac function. Prior to arrival at our unit, the patient was admitted to a local community hospital with a working diagnosis of schizophrenia after she was found to have homicidal ideation. She was at this hospital for over a month, where she has continued on her home medications of Flecainide 100 mg BID and metoprolol 25 mg daily. She was also given lorazepam PRN for agitation but received no treatment for her schizophrenia, as any medication that would prolong her QT interval could cause a potentially fatal arrhythmia. The hospital's inpatient Cardiology and patient's outpatient cardiologist were both consulted, and it was recommended that the patient could only be safely treated with neuroleptic medication if she was on continuous cardiac monitoring.

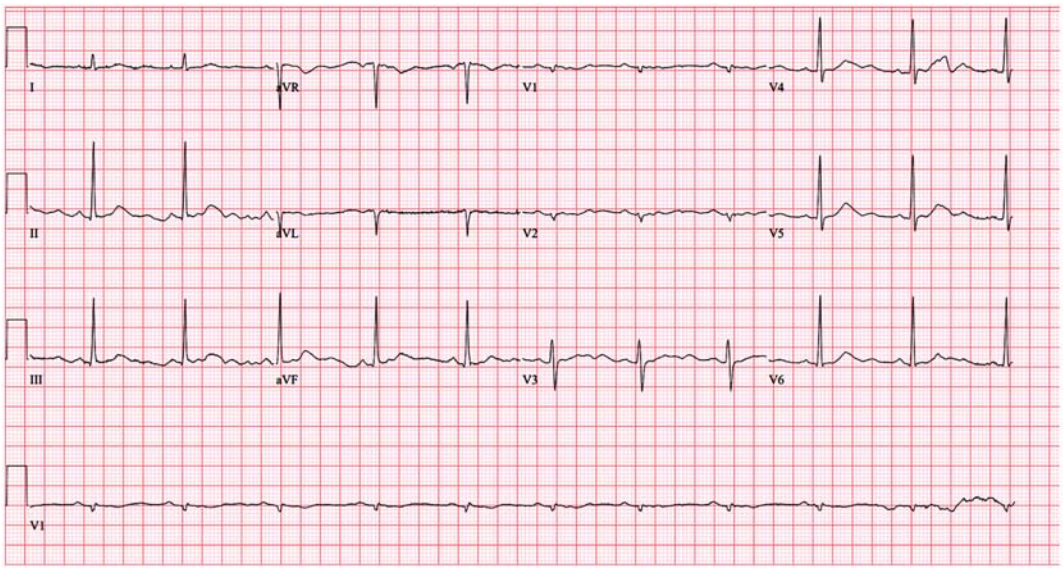
The patient first presented to a cardiologist at the age of 23 for the management of her bidirectional ventricular tachycardia. Her cardiac history began at the early age of 8, at which time she was diagnosed with an episode of severe bronchitis and was noted to have ventricular ectopy on an EKG. Pediatric notes prior to the age of 8 had noted a normal cardiac exam and documented normal cardiac rhythm. She subsequently underwent a routine physical exam at the age of 15 prior to starting high school, during which time a 12-lead EKG was done, demonstrating bidirectional ventricular tachycardia. She was diagnosed at that time of probably having had a prior episode of myocarditis. Based on these ECG findings, she was advised to curtail her exercise regimens. She moved to Russia at the age of 20 and, while there, had a Holter monitor, which showed significant ventricular ectopy with nearly 40,000 extra beats. She returned to the United States 3 years later and had several cardiology visits for persistent episodic palpitations that failed treatment with B-Blockers, calcium channel blockers, and amiodarone. Over the next 8 years, the patient continued to have episodes of palpitations with PVCs, atypical chest pain, and paroxysmal ventricular tachycardia. At the age of 31, she had DNA testing and was found to have a mutation in the *KCNJ*2 gene and given the diagnosis of Anderson-Tawil syndrome.

She was admitted to the inpatient service, and Cardiology was consulted. The decision to start the neuroleptic medication was put into action with the patient

receiving Zyprexa (olanzapine) 10 mg PO every night along with Ativan (lorazepam) 2 mg PRN. Her initial potassium and magnesium were low and were repleted and kept on the higher end of the normal reference ranges before initiation of therapy. Over the course of a few days, she was slowly up titrated to 15 mg daily with improvement in her psychotic symptoms. The patient had EKGs twice daily and was also on continuous cardiac monitoring. Her Qtc ranged from 440 s to 470 s which seemed to be consistent with her baseline readings (Figure 1). There was no ventricular arrhythmia during her telemetry stay and hospitalization. On discharge, she was linked to an outpatient clinic for psychiatric follow-up.



(a)



(b)

Figure 1. ECG before (a) and after up-titration to 15 mg of olanzapine (b). Both show normal sinus rhythm with a rate of 60 - 75 beats per minute. Initial QTC of 457, which lengthened to 482 after olanzapine.

3. Discussion

Andersen-Tawil syndrome (ATS) is a form of periodic paralysis which is a set of rare neuromuscular disorders that are inherited in an autosomal dominant pattern. They cause mutations in skeletal muscle sodium, calcium, and potassium channel genes. They usually present in the 20 s or 30 s with episodic flaccid weakness, brought on by diet or rest after exercise [6]. Anderson-Tawil syndrome has a characteristic clinical presentation of episodic flaccid muscle weakness (*i.e.*, periodic paralysis); ventricular arrhythmias and prolonged QT interval. There are associated physical anomalies including low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis [4] [7]. It has been linked to mutations in the *KCNJ*2 genes on chromosome 17q23 which encodes the alpha subunit of the K^+ channel protein Kir2.1 (ATS type 1) that is expressed in skeletal muscle, heart, and the brain [6] [7]. The diagnosis of ATS can be difficult due to its high degree of phenotypic variability and significant non-penetrance in individuals with a *KCNJ*2 mutation [7]. The triad of paralysis, arrhythmias, and phenotypic characteristics has been reported in 58% - 78% of patients with a confirmed mutation while 32% - 81% of individuals have any two features of the triad [7]. The clinical diagnosis of ATS is made when individuals have two of three clinical features of the syndrome or have one of the three features as well as a family member with two of the three criteria [6]. The diagnosis of ATS is established in individuals with clinical characteristics and ECG findings that support the diagnosis of ATS or by identifying a pathogenic variant in the *KCNJ*2 gene [6]. However, a mutation in the *KCNJ*2 gene is estimated to be present in only 60% of patients with ATS [7].

Cardiac involvement is a major feature of ATS. A prolonged QT is seen in 50% of patients with ATS. Additionally, 84% of patients have ventricular arrhythmias, with bidirectional ventricular tachycardia (BVT) being the most common rhythm abnormality and is found in 32% of patients. Cardiac arrest can occur in around 10% of patients with ATS. Finally, patients may have ECG findings that reflect abnormalities in repolarization. These include a prolonged terminal T-wave downslope, biphasic and large U waves, and a wide TU wave pattern. These ECG findings may be absent in patients with clinical ATS but with no mutation in the *KCNJ*2 gene [5]. Annual screening with a 12-lead EKG and 24-hour Holter monitor for asymptomatic individuals with a *KCNJ*2 pathogenic variant is recommended [8].

Accurate QT measurement may be challenging because the presence of U waves makes it difficult to determine the end of the T-wave, but the QT interval can be easily measured using the "tangent method" if automated measurement is not available or appears incorrect (**Figure 2**). Correct QT measurement is key to minimizing the risks of over- or under-estimating the QT interval and wrongly stratifying patient risk. To minimize inconsistencies, it is best to measure the tangent of the descending T-wave to baseline in leads II or V5. This technique has been found to be the most reproducible among experts and non-experts alike [9].

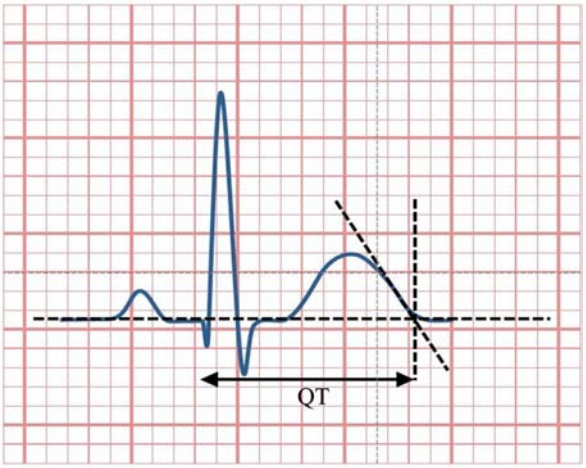


Figure 2. Cartoon showing measurement of the QT interval, (Own work, peaBrianC) [10].

The most widely used formula for calculating the QTc is the Bazett formula, given by $\mathrm{QTcB} = \mathrm{QT}/\sqrt{\mathrm{RR}}$. RR denotes the length of time between the QRS complexes (the RR interval). It is commonly abbreviated as QTcB. Barret formula is inaccurate for heart rates that are not in the normal range but it still remains the most used due to the lack of a widely accepted technique and is often reported on ECG machines [9]. For patients with a higher heart rate, the Fridericia correction formula is suitable (QTc = QT/RR0.33). The normal patients, the normal value of the QTC length is around 400 ms (can reach up to 460 ms for women and 450 ms for men), and QTc intervals longer than 500 ms are considered to be a major risk factor for the development of Tdp [11].

The approach to pharmacological interventions consists of therapy to abort acute attacks and chronic preventive therapy to reduce attack frequency. The cornerstone of treatment of patients with congenital prolonged QT involves avoiding drugs that prolong QT and the use of antiadrenergic therapy with B -blockers is a class I recommendation for all symptomatic, and asymptomatic patients with QT ≥ 470 ms. Left cardiac symptomatic denervation is recommended in patients in whom B-blockers are not effective, contraindicated or not tolerated. This is also the recommendation for patients who refuse or are unable to get implantable cardioverter-defibrillator or beta blockers [12]. For patients with reduced left ventricular function with significant, frequent ventricular arrhythmias, empiric treatment with flecainide should be considered and has been shown to suppress exercise-induced ventricular arrhythmia [13].

The treatment of patients on antipsychotics depends on the type of antipsychotic drug and the severity of QT duration (**Table 1** and **Table 2**) [14]. The use of ICD in patients with schizophrenia may be difficult and depend on their ability to tolerate the ICD. Due to this, the decision to implant an ICD is not straightforward.ICD is indicated as primary prophylaxis is used in patients with non-sustained torsades de pointes or persistent prolonged QTC (e.g. >550 ms) or discontinuing medication that caused the prolonged QT is impossible [14].

Table 1. Effect of antipsychotic drugs in QT.

The effect of psychotropics on QTc	
No effect:	Brexipiprazole, Cariprazine and Lurasidone
Low effect (Overdose or <10 ms increase in QTc)	Aripiprazole, amisulpride, clozapine, flupentixol, fluphenazine, perphenazine, prochlorperazine, olanzapine, risperidone, sulpiride, loxapine, paliperidone
Moderate effect (>10 ms QT prolongation at clinical doses)	Amisulpride, chlorpromazine, levomepromazine, iloperidone, melperone, quetiapine, ziprasidone
High effect (>20 ms QTc prolongation at average clinical doses)	Pimozide, Sertindole Any single drug or combination of drugs that are used in doses above recommended upper limits

Table 2. QTc duration severity and appropriate treatment.

QTc < 440 ms (Men) or <470 ms (Women)	No action required unless abnormal T-wave morphology—consider cardiac review if in doubt.
QTc > 440 ms (Men) or >470 ms (Women), but <500 ms	Consider reducing dose or switching to drug of lower effect; repeat ECG and consider cardiology review.
QTc > 500 ms	Stop suspected causative drug (s) and switch to drug with a lower effect: immediate cardiology review is needed. If the patient has syncope or pre-syncope, immediate ECG monitoring for ventricular arrhythmias should be performed.
Low-risk antipsychotics lurasidone,	cariprazine or brexpiprazole.

4. Conclusion

Anderson Tawil syndrome is a congenital long QT syndrome that presents with cardiac arrhythmia and may lead to sudden cardiac death. Drugs that prolong the QT level are always avoided as much as possible for these patients. Our patient with Anderson Tawil syndrome developed schizophrenia and needed a neuroleptic drug to control her symptoms. Under the supervision of both psychiatrist and cardiologist with telemetry evaluation, the patient was treated and discharged. We recommend the development of appropriate treatment guidelines for treating patients with Prolonged QT who needs neuroleptics.

Informed Consent

Informed consent was taken from the patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Identification of Novel Nonsense *RPGR* Variant Causing Mild X-Linked Cone-Rod Dystrophy and Myopia

Kunka Kamenarova[1,2], Sylvia Cherninkova[3], Kalina Mihova[1,2], Rosen Georgiev[4], Yana Nikolaeva[5], Radka Kaneva[1,2]

[1]Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical Faculty, Medical University—Sofia, Sofia, Bulgaria
[2]Laboratory of Genomic Diagnostics, Department of Medical Chemistry and Biochemistry, Medical Faculty, Medical University—Sofia, Sofia, Bulgaria
[3]Clinic of Nervous diseases, University Hospital "Alexandrovska", Sofia, Bulgaria
[4]Clinic of Eye Diseases, University Hospital "Alexandrovska", Sofia, Bulgaria
[5]Eye Clinic "Vision", Sofia, Bulgaria
Email: kkamenarova@yahoo.com

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Abstract

Background: Mutations in the *RPGR* gene are associated with rod-cone or cone-rod dystrophy, the latter associated with mutations at the distal end. Cone-rod dystrophy (CRD) is a subgroup of hereditary retinal disorders characterized by the primary degeneration of cone photoreceptors often followed by progressive loss of rod photoreceptors in the peripheral visual field. Purpose: The aim of this study was to describe the milder CRD phenotype associated with a novel pathogenic variant c.1905 + 223C > T (p.Q710X) found in *RPGR* which results in shortening of the photoreceptor specific isoform *RPGR* ^{ORF15}. Method: An 11-year-old boy with symptoms of CRD and two female relatives were referred for detailed ophthalmic examinations. Genetic testing was performed by next-generation sequencing of clinical exome followed by Sanger sequencing for segregation analysis. Results: Genetic analysis identified a novel variant in ORF15 of the *RPGR* gene (c.1905 + 223C > T, p.Q710X) in the proband considered as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) standards. Segregation study identified the mutation in a heterozygous state in the mother and her sister. Detailed ophthalmological examination revealed slightly reduced color vision and scattered grayish point-like deposits in the posterior pole of the fundus in the male patient. All mutation carriers were myopic. Conclusion: We report a novel pathogenic *RPGR* variant in a Bulgarian patient with clinical features compatible with the CRD diagnosis. This condition is inhe-

rited as an X-linked dominant trait in its familial form presenting with a mild CRD phenotype in the male hemizygous proband and a moderate to high myopia in the female heterozygous carriers.

Keywords

Cone-Rod Dystrophy, Myopia, *RPGR*, Novel Mutation

1. Introduction

Cone-rod dystrophy (CRD) is an inherited retinal disorder (IRD) with prevalence 1 in 40,000, characterized by visual loss, color vision defects, decreased sensitivity in the central visual field, and a variable degree of nystagmus and photophobia. It represents an important cause of visual impairment in children and adults. CRD is characterized by progressive loss of cone photoreceptor function followed by progressive loss of rod photoreceptor function and is often accompanied by retinal degeneration [1]. Over time, affected individuals develop night blindness and loss of peripheral field. At end stage, CRD may not differ from the rod-cone dystrophies, also called retinitis pigmentosa (RP, with prevalence of 1 in 4000) [2]. Typically, fundus imaging of CRD patients presents pigmentary deposits resembling bone spicules (often in macular or paramacular area), retinal vessels attenuation, pale optic disc and various degrees of retinal atrophy [2]. Progressive degenerative changes of the macula occur rarely. X-linked cone-rod dystrophy (XLCRD) is a rare progressive retinal degeneration and usually manifests with early visual impairment affecting predominantly male patients (hemizygotes), who are legally blind before the end of their third decade, while carrier heterozygous women present various degrees of visual dysfunction, ranging from asymptomatic to severe phenotype [3]. The retinas of some affected males had a bronze-green tapetal-like sheen. The degree of rod-photoreceptor involvement can be variable, with degeneration increasing as the disease progresses. Although penetrance appears to be nearly 100%, there is variable expressivity with respect to age at onset, severity of symptoms, and findings [4]. Moderate or high myopia is often secondary to XLCRD phenotype both on patients and carrier [5].

RPGR gene is a major cause of X-linked retinitis pigmentosa (XLRP) which is the most severe type of RP (OMIM #300029), and is also responsible for XLCRD (OMIM #304020) and atrophic macular degeneration (OMIM #300834) [6]. The *RPGR* gene encodes the retinitis pigmentosa GTPase regulator (RPGR) protein and is able to express multiple retinal isoforms through alternative splicing. The two major isoforms include $RPGR^{1\text{-}19}$, which spans exons 1 - 19 and encodes an 815-aa polypeptide, and $RPGR^{ORF15}$, which spans exons 1 - 15 plus a part of intron 15 and encodes a 1152-aa polypeptide [7] [8]. It shares exons 1 - 14 with $RPGR^{1\text{-}19}$ plus the exon ORF15, encoding 567 amino acids with a repetitive glycine and glutamic acid-rich domain and a conserved basic C-terminal domain.

In addition to these two major transcripts of the gene, *RPGR* encodes complex alternative spliced transcripts and many novel tissue-specific exons have been reported. All of the transcripts encode an amino (N)-terminal RCC1-like domain that is structurally similar to the RCC1 protein, a guanine nucleotide exchange factor for the small GTP-binding protein, Ran [9]. *RPGR* $^{1\text{-}19}$ is widely distributed in ciliated tissues, whereas *RPGR* ^{ORF15} is found primarily in the connecting cilia of photoreceptor cells, predominantly in the outer segment of rod photoreceptors [10]. Due to the presence of highly repetitive purine-rich sequences, the exon ORF15 is a mutational hotspot for XlRP (accounting for 2/3 of all disease-causing mutations) and for most XLCRD cases [11].

Most reported mutations in the first 14 exons are nonsense or frameshift mutations that can lead to nonsense-mediated decay of the mRNA (NMD), and low or absent levels of the transcript. In contrast, nonsense or frameshift mutations in ORF15 are less likely to lead to NMD since this is the last exon of the transcript [12], and a series of truncated proteins of varying length can be found [13].

From a genetic point of view, IRDs displays locus and allelic heterogeneity, with more than 300 causative genes (https://sph.uth.edu/retnet/) that make the genetic characterization very difficult. The advent of next-generation sequencing (NGS) has opened new frontiers in genetic diagnostics of IRDs, exploiting the high-throughput parallel sequencing and the simultaneous analysis of many samples. The overall mutation detection rate for IRDs is variable and ranges from 36% to 60%, leaving many cases still genetically unsolved [14]. Although whole-exome sequencing (WES) is a more appropriate tool for genetic diagnostics of the extreme heterogeneous IRDs than gene panels, commercialized gene panels comprising all known disease-related genes, called "clinical exome" have been successfully applied for genetic testing of retinopathies [14] giving a diagnostic yield of over 80% for IRD cases in Bulgaria (personal unpublished data).

Here, we describe a male patient with clinical suspicion of CRD in whom clinical exome sequencing (CES) found a novel nonsense mutation in the exon ORF15 (c.1905 + 223C > T, p.Q710X) of *RPGR* gene. The presence of *RPGR*-c.1905 + 223C > T variant in the myopic female carriers is consistent with X-linked dominant mode of inheritance and milder phenotype in the studied pedigree.

2. Material and Methods

Patient and clinical assessment

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Medical University of Sofia (Bulgaria). Written informed consent form was obtained from all participants.

An 11-year-old boy complaining from impaired vision, photophobia, and myopia noticed since about 7 years of age, was referred by the University Hospital "Alexandrovska", Sofia. The proband underwent a complete ophthalmic exami-

nation, including autorefractometry after cycloplegia (Canon autorefractometer RK-F2), determination of best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit lamp examination of the anterior eye segment, automated perimetry (Octopus perimeter), slit lamp examination of the ocular fundus using + 90D lens with dilated pupils, multifocal electroretinogram (mfERG, RETIscan Standard 6.11), fundus photograph (Eidon true color confocal scanner), Ishihara color vision test, fundus autofluorescence (FAF, Eidon true color confocal scanner), optical coherence tomography (OCT, NIDEK, RS 3000).

In order to study the genetic basis of the phenotype segregating in this pedigree, we collected peripheral blood samples from the proband for CES analysis as well as from asymptomatic and myopic family members available for segregation study.

Genetic analysis

Peripheral blood samples of the proband, his parents and the sister of his mother (Figure 1) were collected for a molecular genetic analysis and DNA was extracted from leukocytes using Chemagic DNA blood 10 k kit H1 and Chemagen Magnetic Separation Module (PerkinElmer®, Waltham, MA, USA) according the manufacturer's protocol. Targeted NGS was performed using TruSight One sequencing panel (Illumina, San Diego, CA, USA), which includes 4813 genes associated with known OMIM diseases. TruSight one sequencing

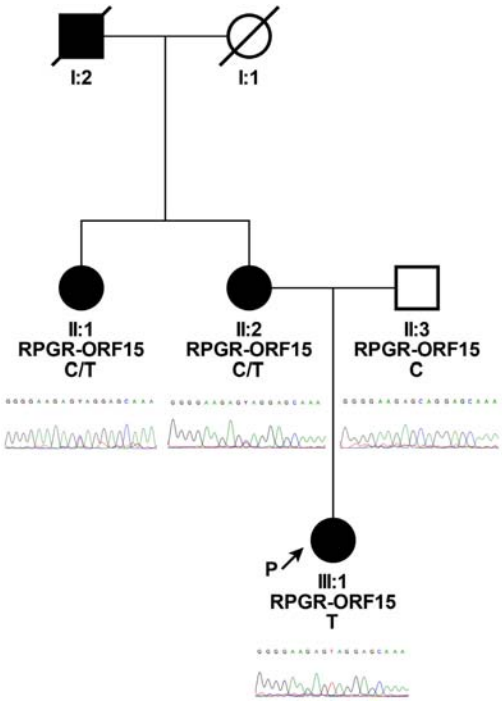


Figure 1. Pedigrees of CRD family and segregation analysis of identified c.1905 + 223C > T in *RPGR* ^{ORF15}. Individuals are identified by pedigree number. Squares indicate males, circles indicate females, slashed symbols indicate deceased, solid symbols indicate affected individuals, open symbols indicate unaffected individuals, black arrow indicates the proband. Sequencing chromatograms showing mutation segregation in each pedigree is presented.

panel includes all reagents required for amplification, amplicon enrichment, and indexing of samples, and protocol was followed according to the manufacturer's instructions. After preparation of the sequence libraries, MiSeq next-generation platform (Illumina) was used to sequence 150-bp paired-end reads.

Assessment of the pathogenicity of candidate variants

Filtered variants with coverage < 20× and those with MAF higher than 0.005 (in case of presumed autosomal recessive mode of inheritance) in at least one of the searchable databases (dbSNP or gnomAD) were excluded. To detect known disease-associated mutations, the remaining variants were compared to human mutation databases such as HGMD and ClinVar. The pathogenicity of novel SNVs was predicted by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.bii.a-star.edu.sg), MutationAssessor (http://mutationassessor.org/r3/), and FATHMM (http://fathmm.biocompute.org.uk/) softwares. Pathogenicity of variants was ascertained according to the criteria of American College of Medical Genetics (ACMG) [15], which classify variants according to 5 categories (benign, likely benign, uncertain significance, likely pathogenic, and pathogenic).

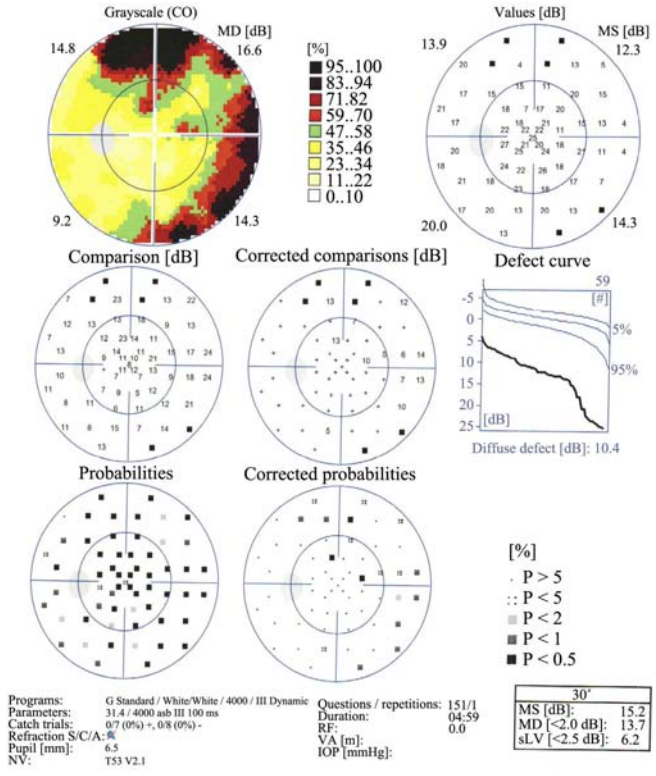
The Identified variant was confirmed by Sanger sequencing on an ABI 3130XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The DNA fragments containing the variants were amplified by PCR with specific primers and were sequenced using the Big Dye 3.1 Terminator Sequencing Kit. Sanger sequencing was also employed for segregation study.

3. Results

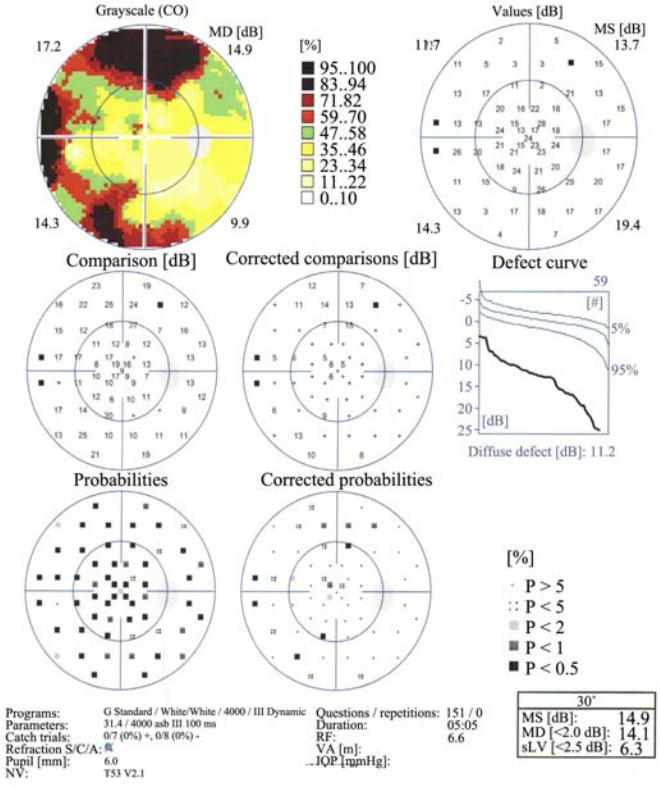
Clinical data

Patient has suffered from symptoms consisting with a mild form of CRD, including decreased sensitivity in the central and peripheral visual field, slightly reduced visual acuity, and myopia with no nyctalopia and color vision defects observed. BCVA was declined to 0.7 (metric) in both eyes (with spherical correction of −1.0 D in the left eye). Automated perimetry showed a bilateral peripheral and central perimetric defect (**Figure 2(a)** and **Figure 2(b)**). Ophthalmic examination revealed grayish point-like deposits scattered within the posterior pole of the fundus, mainly in the paramacular area, but no attenuation of the retinal vessels, optic disc pallor and retinal atrophy were observed (**Figure 3(a)** and **Figure 3(b)**). Fundus autofluorescence did not reveal a pathologic finding (**Figure 4(a)** and **Figure 4(b)**). The optical coherence tomography showed normal retinal thickness and absence of any pathological changes (**Figure 5(a)** and **Figure 5(b)**). The Ishihara test revealed no abnormalities in color perception. ERG profile of the proband demonstrated normal morphology and polarity with a reduced amplitude of scotopic and photopic response (20% for the right eye and 25% for the left eye) and prolonged latency (**Figure 6**).

Patient's mother (II: 2, 44 y) and her sister (II: 1, 50 y) presented with moderate (−4.0 diopters) and high myopia (−8.0 diopters), respectively, from their

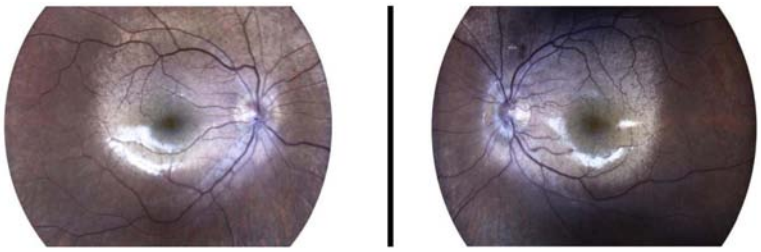


(a)



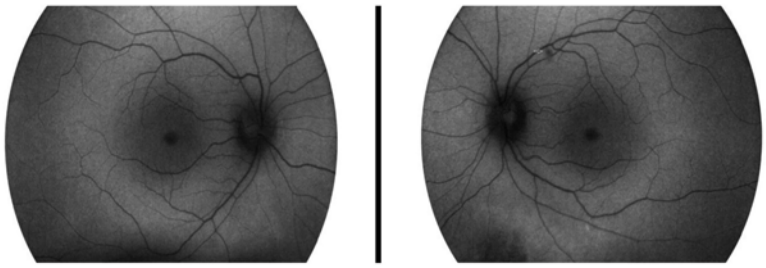
(b)

Figure 2. A bilateral peripheral and central perimetric defect in the 11-year-old proband ((a)—right eye, (b)—left eye).



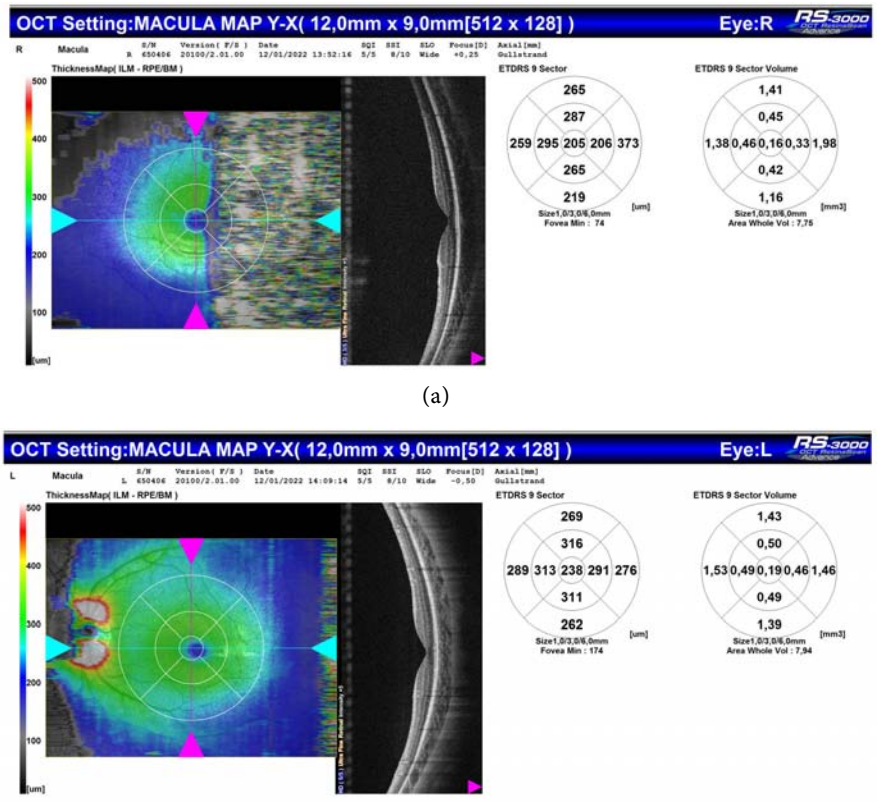
(a) (b)

Figure 3. Fundus photograph (Eidon true color confocal scanner) in the 11-year-old proband ((a)—right eye, (b)—left eye, white arrow—artifact from vitreous opacity).



(a) (b)

Figure 4. Fundus autofluorescence in the 11-year-old proband ((a)—right eye, (b)—left eye, white arrow—artifact from vitreous opacity).



(a)

(b)

Figure 5. Optical coherence tomography in the 11-year-old proband ((a)—right eye, (b)—left eye).

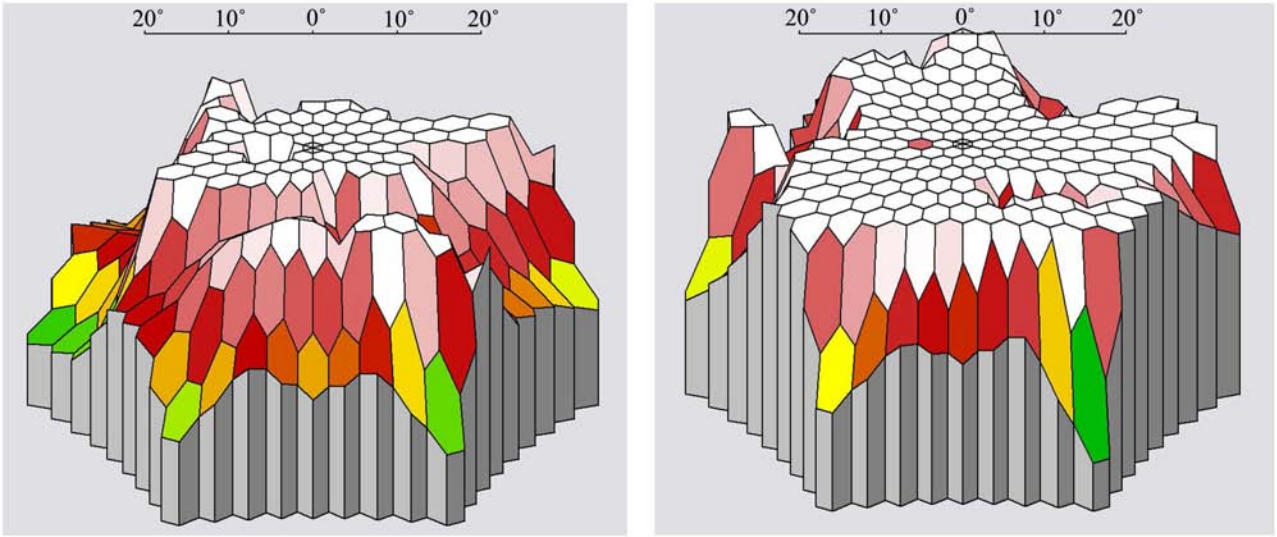


Figure 6. Multifocal ERG in the 11-year-old proband ((a)—right eye, (b)—left eye).

20s. Fundus and electrophysiological examination of the two sisters (II: 1 and II: 2) showed no abnormalities. The ophthalmic diagnostic data are documented in Table 1. There was no older male carrier available for study the progression during follow-up years.

Genetic findings

Family pedigree is shown on Figure 1. Genetic testing of proband's DNA identified a novel variant c.1905 + 223C > T (p.Q710X) in the *RPGR* ^{ORF15}. The mean sequence coverage was over 100× and more than 95% of target bases were covered with at least 20×. A novel variation, c.1905 + 223C > T, in *RPGR* gene resulting in a stop codon and premature translational termination at position 710 (p.Q710X) of the normal 1152-aa polypeptide was identified as the potential disease-causing nonsense mutation. The novel *RPGR* variant has not been reported in the context of clinical significance (ClinVar, HGMD) and is not found in the gnomAD population database and dbSNP. According to the ACMG classification, c.1905 + 223C > T (NM_001034853.1) was classified as a pathogenic because of 1) its type of null variant (PVS1), 2) absence in healthy individuals (PM2), 3) co-segregation with the disease in the family (PP1), 4) occurrence in a gene that has a low rate of benign missense variation (PP2), 5) computational tools predict a deleterious effect on the coded gene product (PP3) and 6) phenotype and family history specific for X-linked disease with a monogenic etiology (PP4).

Genomic DNA of collected family members was further analyzed by Sanger sequencing. Novel *RPGR* variant c.1905 + 223C > T was confirmed for the proband as a hemizygous mutation and for the myopic female members (mother and aunt) who were heterozygous carriers (Figure 1). The change was not found in the unaffected father. Therefore, the novel *RPGR* change c.1905 + 223C > T was shared by affected patients.

Table 1. Clinical characteristics of patients included in the study.

Subject No.	Age at the First/Last Examination (years)	Age at Onset	BCVA (Decimal)	Intraocular pressure (mmHg)		Ishihara	Refraction (Diopter)		Visual Field	Fundus features	Fundus autofluorescence	OCT		mfERG	
			BE	RE	LE	BE	RE	LE	BE	BE	BE	BE	RE	BE	LE
III: 1	7/11	Childhood: Photophobia, refraction error (myopia), reduced visual acuity, impaired central vision	0.7	11.3	10.5	Normal	Normal	−1.0	Paracentral scotoma	Scattered grayish point-like deposits in the posterior pole mainly in the paramacular area, normal optic discs and retinal vessels	Normal	Normal retinal thickness and absence of pathological changes	Reduced amplitude of 20%	Reduced amplitude of 25%	
II: 1	20/50	Childhood: No complains. Early 20s: Refraction error (myopia)	1.0	Not tested	Not tested	Normal	−8.0	−8.0	Normal	Normal	Not tested	Not tested	Not tested	Not tested	
II: 2	20/44	Childhood: No complains. Early 20s: Refraction error (myopia)	1.0	Not tested	Not tested	Normal	−4.0	−4.0	Normal	Normal	Not tested	Not tested	Not tested	Not tested	

Abbreviation explanation: LE - Left Eye, RE - Right Eye, BE - Both Eyes, BCVA - Best Corrected Visual Acuity, OCT - Optical Coherence Tomography, mfERG - multifocal Electroretinography.

4. Discussion

XLCRD is a rare, progressive inherited retinal degeneration which primarily affects the cone photoreceptors. In affected men the disease is characterized by early onset (childhood) and rapid progression of vision loss, resulting in legal blindness by the end of 30s. In contrast to men, most affected women show extremely variable symptoms, ranging from asymptomatic electrophysiological abnormalities to severe retinal disease [16], and legal blindness occurs at approximately 30 - 40 years of age [17]. Inactivation of the X chromosome is believed to contribute to more severe phenotype [18], however, presence of other modifying genetic factors has also been discussed [19]. According to literature, *RPGR* carriers are most likely to present symptoms that might be grouped in four main patterns of fundus appearance: normal or near normal pattern, a tapetal reflex, focal or patchy pigmentary retinopathy limited to a quadrant or hemisphere, and three or more quadrants of bone spicule pigmentation or atrophy [20]. Most patients complain of myopia, with 50% - 72% having a refractive error of greater than −6 diopters [21].

RPGR is a major locus for XLCRD. Mutations that cause CRD are predominantly located at the 3' end of the ORF15 exon in *RPGR* [22]. *RPGR* is expressed in retinal photoreceptors where it is located in the connecting cilia of both rods and cones [23] and being a regulator of protein trafficking, RPGR is involved in maintaining the structure and function of mature cilia. Defects in *RPGR* result in a severe retinal ciliopathy, which finally leads to retinal degeneration [24].

In this study, we report a Bulgarian family affected by XLCRD. Detailed clinical diagnostic data describing the phenotype of the proband are presented. Genetic analysis identified a novel hemizygote nonsense variant (c.1905 + 223C > T, p.Q710X) in *RPGR* gene that co-segregates with the heterozygote female carriers as high myopia. Thus, the variant p.Q710X in *RPGR* represents a novel disease-causing mutation leading to mild X-linked CRD in male and moderate to high myopia in female patients.

The nonsense mutation (c.1905 + 223C > T, p.Q710X) identified in this study is located in exon ORF15, considered the major disease-associated locus due to its highly repetitive purine-rich sequence [25]. The c.1905 + 223C > T mutation is localized before the repetitive glycine and glutamic acid-rich domain (AD) and similar to other previously described variant would result in shortening of RPGR polypeptide by removing the Glu-Gly rich domain and the conserved basic C-terminal domain (BD) [22]. The nonsense mutation that authors have reported creates a truncated protein and the shortened protein did not contain the Glu-Gly rich domain. The N-terminal RCC1-like domain, which plays a role in *RPGR* localization to cilia by binding to *RPGRIP1* and *RPGRIP1L* [26], and also mediates complexation of *RPGR* with SMC1/3, PDEδ, and Rab8, which are critical to cilia functions [9], is preserved in the truncated mutant.

Previous report from Wang *et al.* demonstrated that the hemizygous males who carried a newly found mutation c.2383G > T (p.E795X) in exon ORF15 suffered from typical for CRD symptoms such as early nyctalopia, progressive visu-

al impairment, color vision defects and decreased sensitivity in the central visual field, followed by progressive loss in peripheral vision. Female carriers showed normal phenotype [22]. In contrast to this report, the patient described here presents a mild phenotype including decreased sensitivity in the central and peripheral visual field, slightly reduced visual acuity, and myopia with no nyctalopia and color vision defects observed. There was no history of retinal disease in female carriers except for myopia seen in the mother and her sister. Nevertheless, the female carriers were not examined thoroughly at our institution therefore a mild retinal phenotype cannot be excluded.

It has been previously shown that a novel C-terminal extension variant c.3457T > A (X1153Lext * 38) due to the loss of the terminal *RPGR* ^{ORF15} codon is associated with myopia and adult-onset cone dystrophy in three patients. Considering that the mutation in the last codon resulted in cone-dystrophy in the three patients the authors hypothesize that the involvement of rods diminishes downstream of the ORF15 exon. In addition, it is possible that the cone involvement increases simultaneously with the decrease of rod involvement or else is present at the same level in all phenotypes and becomes more prominent with diminished rod involvement [20]. This is comparable to our observation, as our patient had myopia and typically early central vision decrease. Minimal progression during the follow-up 4 years suggests a relatively stable disease after the initial impairment of the central vision.

Given the complexity of *RPGR* function and network, the pathogenic mechanism resulting from *RPGR* mutations remains to be clarified. It remains unclear until now why some mutations in *RPGR* cause RP and others cause CRD. Literature on why some ORF15 mutations affect rods, and others cause predominantly cone degeneration is published [27]. It seems attractive to speculate that mutations in the exon ORF15 are more often found in CRD cases, whereas mutations in the exon 1 - 14 are more often found in RP [22] [28].

5. Conclusion

In summary, our findings have identified a novel point mutation in the terminal codon of *RPGR* ^{ORF15}, c.1905 + 223C > T, p.Q710X, that contributes to a milder phenotype consistent with X-linked CRD (in hemizygotes) and moderate to high myopia (in heterozygotes) and further broadens the spectrum of *RPGR* mutations.

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Disclosure Statement

The authors report no conflict of interest.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Case Report of Cardiac Tamponade Due to Acute Chagas Disease after Misdiagnosis of Visceral Leishmaniasis Based on Serology

Valéria R. Corrêa[1*], Welyda R. Lima[1], Luis. F. D'A. e Castro[1], Heitor F. A. Junior[2], Marina C. Affonso[3], Leonardo P. N. Silva[4]

[1]Department of Medicine, Hospital Regional de Araguaína, Araguaína, Brazil
[2]Department of Pathology and Protozoology Laboratory, FMUSP, São Paulo, Brazil
[3]Department of Medicine, Faculty of Medicine São Caetano do Sul, São Caetano do Sul, Brazil
[4]Department of Medicine, Centro Universitário Tocantinense Presidente Antônio Carlos, Araguaína, Brazil
Email: *lu_val@uol.com.br

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Abstract

Protozoan diseases such as Visceral Leishmaniasis (VL) have re-emerged in Northern Brazil and cases of Chagas Disease also occur. This VL increase leads to early therapy for the public. Confirmatory parasitological diagnoses in VL are performed by bone marrow or spleen aspiration, but ELISA, IFA or immunochromatographic tests for antibody detection are easily performed and can be used in the presence of clinical signs as confirmatory for specific therapy. This approach is successful in providing therapy and prevention of death in VL, but there is a chance of confusion with the emerging disease, Chagas Disease (CD), due to cross-reacting and similar clinical pictures, as in this case. Both VL and CD presented many asymptomatic or oligosymptomatic cases, complicating the picture. Our case report emphasizes these aspects. Positive serology, with an IIF titer of 1/160, and epidemiological correlation, suggests the diagnosis of VL and imposes antimony therapy. Despite the unfavorable evolution and signs of cardiac involvement, the presence of pericarditis and cardiac tamponade confirmed by the echocardiogram suggests CD. We reassessed the profiles of a suggested CD serology, the diagnosis was corrected and treatment with CD specific benznidazole. The good evolution started with benznidazole corroborates the diagnosis of CD and discards the hypothesis of double infection.

Keywords

Heart, Cardiac Tamponade, Trypanosomiasis Acute, Serology

1. Introduction

Chagas Disease (CD) and Visceral Leishmaniasis (VL) are caused by protozoan parasites of closely related genera [1], with similar antigens. Epidemiology of those diseases in the Brazilian Amazon has undergone significant changes in the last 30 years [2], and exists in areas with occurrence both [3].

Despite adequate control and vectorial CD transmission elimination [4], both are reemerging in Northern Brazil; CD due to alternative forms of transmission, such as oral transmission [5] and VL due to spread of the VL reservoir and vector control problems [6].

The early stages of both diseases presented similar involvement of reticuloendothelial organs, such as spleen and liver, presenting similar inconclusive or absent symptoms in most patients. The clinical picture of these acute diseases is similar, but cardiac involvement is rare in VL [7]. In the acute phase, there is prolonged fever, accompanied by systemic manifestations, such as hepatosplenomegaly, and diffuse myocarditis and acute serous pericarditis may occur, evolving in 48% of patients with pericardial effusion, but cardiac tamponade (CT) is a medical emergency, not frequent and can lead to shock and death [8]. Diagnosis must be the finding of the agents: in blood for CD or in organs aspirates in VL. Those assays demand trained observers.

In our case, the patient was diagnosed with leishmaniasis by serology, with presented cardiac toxicity and demands surveillance with cardiac tests. During those tests, it was detected pericardial effusion and cardiac tamponade. The tamponade was treated adequately by pericardiocentesis with inflammatory pattern.

We emphasize the importance of the differential diagnosis of acute CD in patients suspected of VL in Northern Brazil, endemic areas of leishmaniasis and CD. This warning must be included in VL diagnosis algorithm, reinforcing the diagnosis of other important regional pathologies.

2. Case Report

A 32-year-old man from Santa Tereza—TO, after contact with insect secretions on the ocular mucosa, presented periorbital edema, with fever, lasting approximately 18 days, concomitant with diarrhea and palpitation, being treated with antipyretic and analgesics. Epidemiology was not valued at the time. After approximately 40 days, he developed diffuse adenomegaly, hepatosplenomegaly, lower limb edema and dyspnea, being hospitalized for investigation of the febrile syndrome, with different serologies being performed. Parasitological exams (malaria and CD thick blood smear) and serology for CD (IHA, IIF) and several serologies were performed, with only indirect immunofluorescence for VL being positive (**Table 1**). Treatment with glucan time was started for eight days, at a dose of 20 mg/kg/day.

During hospitalization, he evolved with signs suggestive of cardiac tamponade (CT), confirmed by the echocardiogram that showed CT (**Figure 1**). Transferred

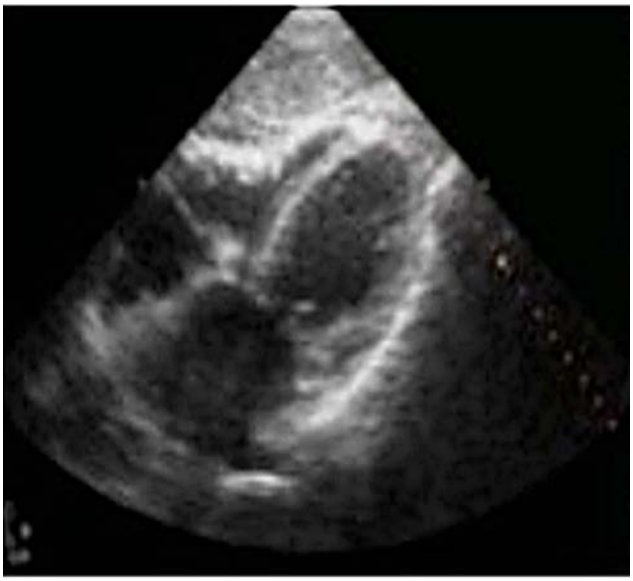

Figure 1. Echocardiogram performed that showed cardiac tamponade.

Table 1. Table of serologies performed in September 2016.

DATE	SEROLOGY	RESULT
2016/09/01	Leishmaniasis	IIF 1/160
	Thick drop Chagas	Negative
	Thick drop Malaria	Negative
	Brucellosis	Negative
	AFB	Negative
	Chagas disease (IHA, IIF)	Negative
	AFB	Negative
	Chagas disease (IHA, IIF)	Negative
2016/09/07	HIV	Negative
2016/09/12	Leishmaniasis rapid test	Negative
	Leishmaniasis	IIF 1/160
2016/09/16	Chagas disease	IIF 1/160 Positive

Note: AFB: Acid-Fast Bacillus; IHA: Indirect Hemagglutination; IIF: Indirect Immunofluorescence; HIV: Human Immunodeficiency Virus.

to the referral hospital, where serologies were repeated, and seroconversion to Chagas Disease (IFI) was evidenced, and the history of contact with triatomine secretion was obtained as patient reports having killed an insect and having contact with the secretion with his eye, without other ocular signs after this. Chest radiography showed an increase in cardiac silhouette (**Figure 2**). The electrocardiogram showed low-voltage QRS complexes, the presence of electrical alternation (**Figure 3**).

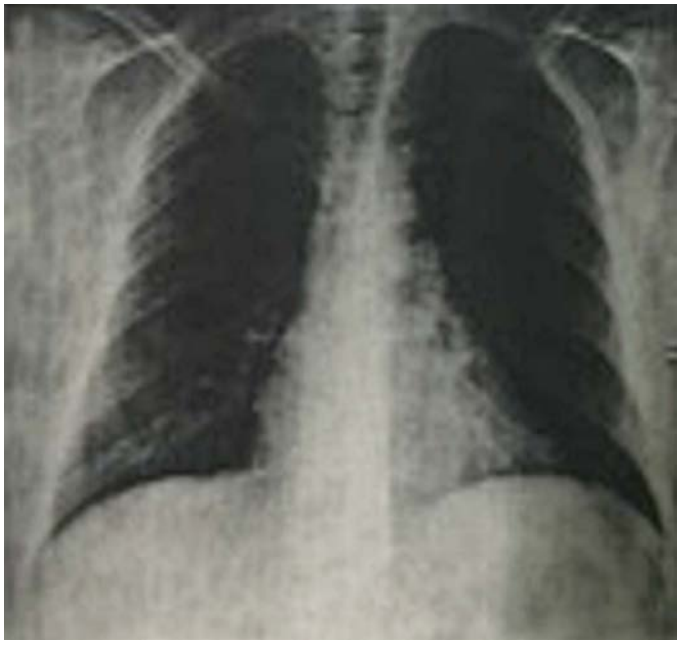

Figure 2. Chest radiography showed an increase in cardiac silhouette.

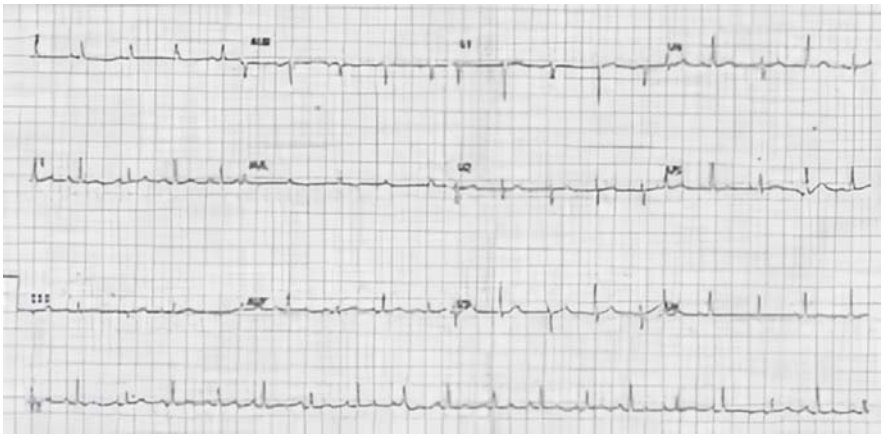

Figure 3. Electrocardiogram performed at suspicion of CD. Note the low amplitude voltage presented in most leads, including signs of electric alternate at the longer D2 lead at lower EKG string.

Relief pericardiocentesis was performed and pericardial fluid analysis show low level lymphocytosis, and absence of microorganisms in a perfusate profile. He started using benznidazole 100 mg orally 3× a day, 09/17/16, as recommended by the Chagas Disease Consensus 2015 6 until completing 60 days, according to the Chagas Disease guidelines. The serological follow-up showed negative serology in six months and the echocardiogram evolved with normalization patterns (Table 2).

Patient evolved asymptomatic, being referred to specific treatment at an outpatient level at the end of benznidazole therapy. Serological and echocardiographic follow-up showed negative serology in six months and the echocardiogram evolved with normalization patterns.

Table 2. Echocardiographic evolution of the heart of the patient in a descriptive table, showing also most of the measures taken for each cardiac area. There is no additional pericardial effusion after benznidazole therapy.

Date	2016/09/15	2016/09/17	2016/11/22
Interventricular septum	13	15	11
Posterior wall	13	14	10
Aortic diameter	36	35	32
Left atrial diameter	45	41	43
Left ventricular diastolic diameter	52	44	55
Left ventricular systolic diameter	34	28	26
Ejection fraction	63	66	83
Obs	Mitral flow with high variability suggesting cardiac tamponade diastolic restriction; Right ventricular collapse	No pericardial effusion	No pericardial effusion
Conclusion	Moderate left ventricular hyper-trophy cardiac tamponade	Moderate left ventricular hypertrophy	Normal

3. Discussion

Protozoan diseases such as VL have reemerged in Northern Brazil and sporadic cluster of CD also occurs. This upsurge of VL cases led to the therapy algorithms by public authorities to facilitate the diagnosis and promote early therapy.

Parasitological diagnoses in VL are performed by bone marrow or risky spleen aspiration. ELISA, IFA or immunochromatographic tests for antibody detection are easily performed and could be used in the presence of clinical signs as confirmatory tests for specific therapy. This approach is successful in providing early therapy and death prevention in VL [9], but there is a chance that another emergent disease, Chagas Disease past sporadic cases remains undiscovered, due to similar serology and clinical pictures [10]. Both VL and DC presented many asymptomatic or oligo symptomatic patients complicating the picture [4]. Meglumine antimoniate is the available therapy for VL nut those antimoniate also could cause cardiotoxicity in a heart already affected by an intense inflammatory process induced by CD, leading to the stormy clinical course.

The recommendation of the Ministry of Health regarding immediate therapy after isolated serology is a problem in areas where Chagas disease and leishmaniasis co-exist. The regional algorithm for febrile syndromes should be expanded, avoiding delays in starting treatment and putting the patient at risk.

The presence of discreet pericardial effusion is frequent in the initial phase of VL (78%), but there is no report of tamponade [11].

Pericardial effusion and tamponade have already been described in CD [7], but not due to diagnostic confusion, where the use of antimony may have corroborated the cardiac damage, complicating its evolution.

Our case report emphasizes those aspects. The positive serology for VL, with an IFA titer of 1/160, and signs and clinical and epidemiological correlation, suggests the diagnosis of VL and imposes antimony therapy. Despite an unfavorable evolution and signs of cardiac involvement, the epidemiology, the presence of pericarditis and cardiac tamponade and seroconversion to Chagas Disease (IIF) suggest CD. We rechecked serology and the antibody profiles now suggested CD, the diagnosis was corrected and treatment with benznidazole 100 mg orally 3× day was started [4]. A satisfactory evolution with benznidazole corroborated the diagnosis of CD and discarded the hypothesis of double infection.

4. Conclusions

The study aims to alert the medical community to the early suspicion of differential diagnoses. The high frequency of febrile syndrome in ACD reinforces the importance of a correct differential diagnosis with other endemic diseases prevalent in the region, which are often neglected due to lack of clinical suspicion, generating an underestimation of the patient's epidemiology and symptoms. delaying diagnosis and specific treatment, which can lead to complications such as in this case.

The clinical case presented was interesting due to the evolution of ACD to tamponade, in a patient who had contact with the secretion of a contaminated triatomine, evolving with CT and considering that no reference was found in the literature consulted to another similar case and was treated with antimony due to false positive for visceral leishmaniasis in their serology.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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ST-Segment Elevation Mimicking STEMI Due to Hypercalcemia: A Case Report

Sicong Yang

Department of Cardiology, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China
Email: yangsicong@sysush.com

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Abstract

ST-segment elevation myocardial infarction (STEMI) is an important, life-threatening diagnosis that requires quick diagnosis and treatment, characteristic ECG of which shows ST-segment elevation. Unfortunately, ST-segment elevation is nonspecific, which can be misleading if not careful to be interpreted, as in this case of hypercalcemia seen by us. A 48-year-old male was admitted to our emergency department with recurrent chest pain, nausea and vomiting. Medical history includes hypertension and diabetes. ST-segment elevation in V1 - V4 mimicking STEMI was present on admission. However, immediate coronary angiography revealed nearly normal coronary arteries, his troponin was negative in 6 hours and calcium was 2.95 mmol/L. It was thought that the ECG changes were not indicative of cardiac ischemia but hypercalcemia. He was managed with calcium reduction treatment such as intravenous normal saline and furosemide, with subsequent resolution of ST-segment changes.

Keywords

Hypercalcemia, Myocardial Infarction, ST Elevation, ECG

1. Introduction

ECG is an important non-invasive test in diagnosis of some severe cardiac diseases such as STEMI, which shows ST-segment elevation and usually requires urgent primary percutaneous intervention. However, ST-segment elevation is nonspecific and may be disease other than STEMI. There are several known mimickers of STEMI that are well documented, but hypercalcemia is rarely mentioned. It's well established that Characteristic ECG changes in hypercalcemia are shortened QT interval, prolonged PR, lengthened QRS interval, flattened or inverted T waves and variable degrees of heart block, few authors have reported

transient ST-segment elevation mimicking STEMI in patients with hypercalcemia. However, as Adam Orville Strand mentioned, hypercalcemia leading to ECG changes consistent with an STEMI is considered very unique but not rare as believed, but only under-reported with a lack of common association [1]. We report a patient with chest pain who showed ST-segment elevation due to hypercalcemia mimicking AMI. By recognizing this, clinicians should take into consideration of more mimickers on ST-segment elevation and prevent adverse outcomes that could easily be avoided.

2. Case Presentation

A 48-year-old male was admitted for recurrent chest pain, nausea and vomiting. He had intermittent retrosternal pain half a month prior, which is more serious after physical activity. An ECG performed in another hospital showed complete right bundle branch block (**Figure 1(a)**), and he refused further diagnosis and treatment. 1 hour ago, he perspired heavily after physical labor, and soon developed nausea, vomiting and fatigue, without chest pain, back pain and dyspnea. ECG in community health unit demonstrated new ST-segment elevation in V1 - V4 (**Figure 1(b)**) concerning STEMI, and patients were sent to our hospital by ambulance after giving 300 mg aspirin,180 mg ticagrelor and 20 mg rosuvastatin calcium.

Medical history includes poorly controlled hypertension that had not been treated medically 5 years before admission, long-term diagnosis of stage 2 diabetes

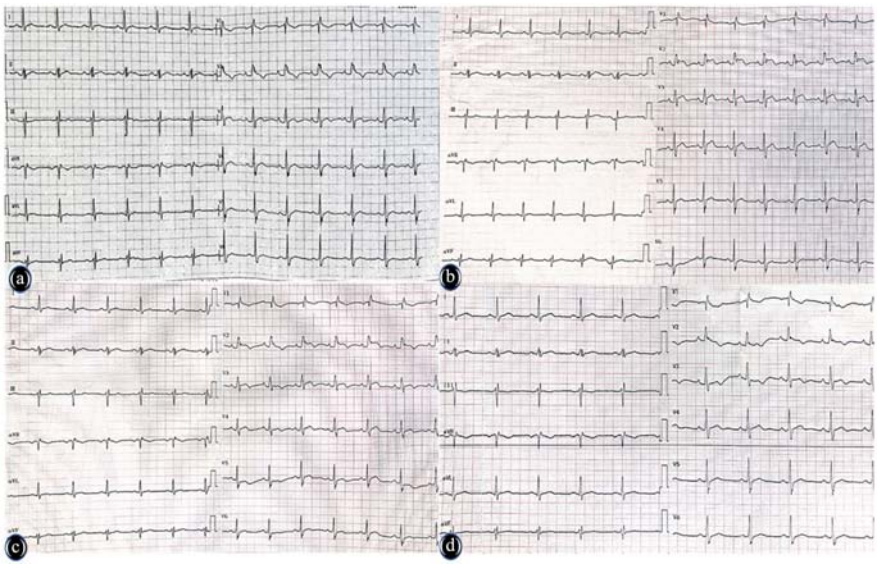

Figure 1. Dynamic ECG evolution of patients: ECG (a) in another hospital suggested incomplete right bundle branch block; ECG (b) in community health unit suggested 0.1 - 0.3 mV of ST-segment elevation in V1 - V4, QoTc 187 ms, QaTc 257 ms, QeTc 351 ms; Postoperative ECG (c) indicated that there was no-dynamic change, QoTc 190 ms, QaTc 268 ms, QeTc 358 ms; Re-examination of ECG (d) on the second day of admission indicated that ST-segment in V1 - V4 returned to normal, QoTc 230 ms, QaTc 312 ms, QeTc 396 ms.

which was controlled by acarbose, not monitoring blood sugar. The patient denied any other history of coronary heart disease, or kidney disease, and never smoked and drank.

In the emergency department, his blood pressure was 130/86mmHg, respirations at 20/min (12 - 20/min), heart rate of 82 beats per minute (60 - 100 beats per min), oxygen saturation of 94% (95% - 100%). There were no pertinent positive physical findings. Given the patient history and the ECG findings, STEMI should be taken into consideration, he undergo urgent coronary angiography, which revealed nearly normal coronary arteries (**Figure 2**).

Subsequently, the first set of cardiac enzymes showed elevated myoglobin 89.99 ng/mL (0 - 58 ng/mL), normal creatine kinase isoenzyme 4.25 ng/mL (0 - 5 ng/mL), troponin negative. All other laboratory values were within normal range except for white blood cell of 12.88 × 10^9/L, of creatinine 213 μmol/L (57 - 111 μmol/L), sodium of 135 mmol/L (137 - 147 mmol/L), chlorine of 93 mmol/L (99 - 110 mmol/L), calcium of 2.95 mmol/L (2.2 - 2.5 mmol/L), glucose of 15.56 mmol/L (3.9 - 6.1 mmol/L). Bedside echocardiography showed no obvious abnormalities 6 hours after the onset, and the second set of cardiac enzymes myoglobin returned to normal, while creatine kinase isoenzyme and troponin I were still negative, and repeated ECG showed persistent marked ST elevation (**Figure 1(c)**), which excluded myocardial infarction as the cause of his electrocardiographic changes. And through searching pertinent literatures, acute renal function injury with hypercalcemia was considered.

The patient was subsequently managed with calcium reduction treatment such as intravenous normal saline and furosemide 20 mg iv. His calcium and creatinine improved progressively (calcium 2.42 mmol/L, creatinine 106 umol/L) on the second day after admission, meanwhile, follow-up ECG showed ST-segment back to baseline in V1 - V4 (**Figure 1(d)**). In addition, his parathyroid hormone was normal.

Over the next few days, the patient's condition improved dramatically. He continued to deny any chest pain or pressure during his following admission and did not deteriorate clinically. He has subsequently discharged home on day four post-presentation.

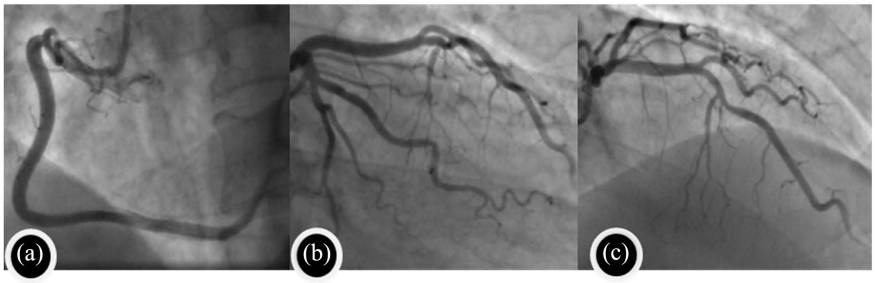

Figure 2. Coronary angiography results of the patient: coronary atherosclerosis in the middle part of the LAD, TIMI grade 3 in the distal blood flow, and no obvious abnormalities in other vessels.

3. Discussion

STEMIs are frequently encountered in hospital visitations and admissions. The earlier the reperfusion therapy is initiated, the greater the benefit. However, there are several known mimickers of STEMI as well as hypercalcemia. Several risks make the diagnosis of the patient STEMI likely: history of diabetes and smoking, chest pain related to physical labor. Eventually, a review after seeing the high-serum calcium levels clarified that ECG changes were all due to acute hypercalcemia.

Hypercalcemia is a common and important clinical problem, most commonly caused by primary hyperparathyroidism and malignant neoplasms, in addition to vitamin D poisoning, sarcoidosis, and other granulomatous diseases [2]. Its clinical manifestations are non-specific, including fatigue, nausea, vomiting, abdominal pain, etc., and can also cause hypovolemia with acute renal injury. The PTH is normal in the patient, who had no special drug taking and no history of tumors causing high calcium. Considering the patient perspired heavily before the onset, the author speculates that dewatering may lead to hypercalcemia.

As is known to all, hypercalcemia can also cause abnormal heart conduction system. The relationship between hypercalcemia and shortened QTc interval is close, including the intervals from the beginning of the QRS to the onset (QoTc), the apex (QaTc), and the end of T wave (QeTc), among which QoTc (<180 ms) and QaTc (<300 ms) have the highest specificity in predicting hypercalcemia [3]. In our case, in the hypercalcemic ST elevated phase, the QoTc and QaTc were 187 ms and 257 ms returned to 230 ms and 310 ms after hypercalcemia was corrected.

In a case-control study published in 2016, Keiko Sonoda, M. D found that J point elevation (including early repolarization and Brugada-type ECG) and ST-segment elevation in hypercalcemia were also common [4]. The patient's ECG was similar to STEMI, and he had risk factors associated with coronary heart disease that more likely led to confusing the diagnosis. ST-segment elevation in hypercalcemia mimicking AMI has been reported in a few cases (Ashizawa *et al.* described a patient with hypercalcemia caused by vitamin D poisoning with "ST-segment elevation" in lead V1 - V2 resembling acute myocardial infarction [5]. Turhan *et al.* reported a case of ST-segment elevation in lead I, II and V1 - V6 [6].) Littman *et al.* reported 16 cases of severe hypercalcemia presented with ST-segment elevation ECG changes in conditions other than AMI [7]. Their ST-segment elevation location was not fixed and was mainly found in the precordial leads. The elevated ST-segments always had a characteristic "scooped" appearance and typically were not followed by distinct T waves. The mean serum calcium was 14.3 ± 2.9 mg/dL and QTc 379 + 44 ms. ST-segment elevation in AMI is often accompanied by prolonged QT interval, ST-segment specular depression, and following characteristic dynamic evolution of ST-segment. The patient did not have typical angina pectoris, the electrocardiogram V1 - V4 was elevated, but the QTc was not prolonged, and there was no obvious specular depression of ST-segment. Troponin I was still normal within 6 hours of onset,

so the diagnosis of AMI was excluded. Of course, the differential diagnosis of ST elevation also needs to consider ventricular tumor, pericarditis, left ventricular hypertrophy, hyperkalemia, etc. Echocardiography and laboratory tests ruled out these possibilities. The ECG recovered after we corrected hypercalcemia.

The mechanism leading to ST-segment elevation in hypercalcemia remains unclear. Studies have shown that shortening QT due to hypercalcemia is mainly caused by shortening the duration of stages 2 and 3. The duration of action potential phase 2 is shortened by inward calcium flow through l-type calcium channels [8]. The higher calcium concentration in the extracellular fluid will promote the rapid influx of calcium through the channel, causing intracellular calcium ions to rapidly reach the threshold of closing l-type calcium channel, reducing the duration of action potential phase 2 [9]. The duration of phase 3 in the action potential is determined by outward potassium flow through delayed recirculating potassium channels [8]. Increased extracellular calcium concentration promotes intracellular entry of calcium ions, possibly activating these potassium channels in the frog heart. This will increase the outward potassium current in stage 3 of the action potential, thus speeding up the repolarization process and thus shortening the overall duration of the systolic phase [10].

4. Conclusion

Clinicians should be aware that high calcium levels may be associated with a pseudo-infarct pattern on the ECG. In patients who are less likely to have acute coronary syndrome, other causes should be explored in a timely manner prior to further intervention. Clinicians must weigh the urgency and risks of intervention against the benefits of waiting for more laboratory results. Nevertheless, if clinical discrepancies make the probability of a STEMI low, it is reasonable to wait for basic laboratories before any type of intervention is pursued. Measurement of QTc interval changes may help in the diagnosis. Dynamic troponin I and electrocardiogram testing are also important in patients with hypercalcemic nephropathy; performing coronary angiography for apparent ST-segment elevation could be harmful because it may result in further deterioration of renal function [11].

Informed Consent

The patient's legal representative has given permission for the publication of this report and the accompanying images.

Conflicts of Interest

The author declares that they have no conflicts of interest pertaining to this article.

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Rituximab for the Treatment of Multiple Sclerosis: A Retrospective Observational Cohort in Morocco

Siham Bouchal[1,2*], Nabila Lahmadi[1], Sara Zejli[1], Naima Chtaou[1,2], Youssef Hafidi[3], Faouzi Belahsen[1,2]

[1]Department of Neurology, Hassan II University Teaching Hospital, Fez, Morocco
[2]Laboratory of Epidemiology, Clinical Research, and Health Community, Faculty of Medicine and Pharmacy, Sidi Mohammed Ben Abdellah University, Fez, Morocco
[3]Department of Pharmacology, Hassan II University Teaching Hospital, Fez, Morocco
Email: *bouchalsiham@gmail.com

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Abstract

Background: RITUXIMAB (RTX) is a chimeric anti-CD20 monoclonal antibody that has initially demonstrated efficacy in patients with B-cell lymphoma. Then, over time, it has demonstrated its efficacy in systemic inflammatory diseases and recently in neurological diseases such as multiple sclerosis (MS). Here we describe our experience with rituximab from one MS center from MOROCCO. **Objectives:** To investigate the safety and efficacy of Rituximab in MS in a Moroccan population. **Methods:** A retrospective uncontrolled observational single-center study from January 2017 to July 2020, was including all off-label Rituximab-treated patients with MS with at least 6 months of follow-up. Outcome data were collected and evaluated relapse rate, EDSS score, and adverse events (AEs) from the medical charts. Adverse events grade according to the Common Terminology Criteria for Adverse Events. **Results:** A total of 63 MS patients were treated with RTX, 47 patients were included, while 12 cases had just initiated treatment and 4 cases were lost to follow-up. The mean age of the patients was 39 ± 12 years with a female predominance (F/M: 1.6). All forms of MS were included, 83% of whom had relapsing-remitting MS. The duration of disease progression was 8 ± 5 years. Median EDSS before RTX initiation was 5.5 (0 - 7). 51% of patients were treated with RTX as second-line therapy after failure of other disease-modifying therapies, whereas 34% received it as first-line therapy. The annualized relapse rates decreased from 0.8 to 0.2 after RTX treatment. The Median EDSS remained unchanged at 71%. Radiological stability was noted in 83.7%, while 13.5% had a single new T2 lesion. Infusion-related AEs occurred during

27.6% of infusions and most were mild. Simple infection grades ≤ 2 were noted in 19%. Abortion occurred in only one patient. **Conclusion:** Our study confirms the usability of rituximab treatment for MS in the MOROCCO healthcare environment.

Keywords

B-Lymphocyte, CD20, Multiple Sclerosis, Rituximab, Moroccan Population

1. Introduction

MS is a chronic inflammatory demyelination disease of the central nervous system. It was first described in 1868 by Jean-Martin Charcot, and since then several forms of the disease have been identified. MS is the commonest non-traumatic disabling disease to affect young adults, especially women. In 2020, an estimated 2.8 million people were affected by MS worldwide [1].

The etiology and pathogenesis of MS remain unclear, and the most likely theory is that genetic susceptibility at birth and exposure to environmental factors during one's life trigger an immune reaction directed against CNS autoantigens [2] [3]. MS has historically been considered an autoimmune disease mediated by $CD4^+$ T cells with an imbalance between helper-1 CNS-reactive effector T cells, Th17, and regulatory T cells [2] [3]. However, an important paradigmatic shift in the immunology of MS has occurred in the past decade. It is now clear the important role of B cells in the pathogenesis of MS [2] [4]. The presence and persistence of oligoclonal bands in the CSF in 90% of patients with MS is also an indirect marker of the involvement of B cells in this theory. The efficacy of anti-CD20 treatments through depletion of B cells has also drawn the attention of researchers to the involvement of B cells in the pathogenesis of MS.

Although its efficacy, safety profile, and treatment regimen in MS are not well codified, RTX is a frequently used off-label anti-CD20 for the treatment of MS in several countries [5] [6] [7]. This work aims to evaluate the efficacy and safety of the use of RTX on a Moroccan population with MS.

2. Methods

Objectives of the study:

- Evaluate the clinical and radiological efficacy of RTX in Moroccan patients with MS.
- Evaluate the tolerance of RTX at the time of infusion and the Adverse events (AEs) recorded since the initiation of RTX. The grades of AEs are according to the Common Terminology Criteria for Adverse Events.

Study protocol:

Monocentric retrospective cohort within the neurology department of hospital university HASSAN II FES, from January 01, 2017, to July 31, 2020, including

47 patients followed for MS and treated with RTX with at least a 6-month follow-up.

- Inclusion criteria:

Patients with a diagnosis of MS according to the McDonalds 2010 and 2017 criteria and treated with RTX with at least 6 months of follow-up.

- Exclusion criteria:
  - RTX start date is recent: less than 6 months follow-up.
  - Patient lost to follow-up.
- To assess clinical effectiveness, annualized relapse rates and Expanded Disability Status Scale (EDSS) scores before and after rituximab initiation were collected from medical records.
- The baseline MRI was defined as the most recent MRI before the RTX initiation. We recorded the presence and number of new lesions in follow-up MRI
- The Adverse events (AEs) recorded since the initiation of RTX was collected from medical records.
- The therapeutic regimen used in our center.
  - Initial 2 doses: 1000 mg intravenous infusions once; repeat dose 2 weeks later.
  - Subsequent doses: 500 mg IV every 6 to 12 months.
  - Premedication: 1 g of paracetamol and L'hydroxyzine (at a dose of 50 mg) orally 30 to 60 minutes before each infusion then direct intravenous injection of methylprednisolone (120 mg) 30 min before starting the rituximab infusion.

Statistical analysis

Statistical analysis was performed using SPSS software. Descriptive results were presented in the form of numbers and percentages for qualitative variables. Quantitative variables were presented in the form of an average accompanied by their standard deviation in the case of normal distribution, otherwise by the median with its extremes. The statistical significance threshold was set at 0.05.

3. Results

75 patients followed in the Neurology department for the demyelinating disease of the CNS, were treated by RTX (n = 63 MS and n = 12 Neuromyelitis Optica).

Among the 63 MS, we excluded 12 MS patients who had just started RTX and 4 who had been lost to sight (Figure 1).

Of 47 patients with MS, the average age was 39 ± 12 years, with a female predominance of 61.7% (n = 29) with a sex ratio F/M of 1.6.

The average duration of disease progression of MS was 8 ± 5 years. The most common progressive form was RRMS in 83% (n = 39). The median EDSS before RTX initiation was 5.5 (0 to 7). The annualized relapse rate (ARR) in the 24 months before RTX initiation is 0.8. The socio-demographic and clinical characteristics of the patient are summarized in Table 1.

Reasons for rituximab initiation among MS patients are described in Table 2. The reasons mainly were lack of efficacy with previous treatment in 24 patients

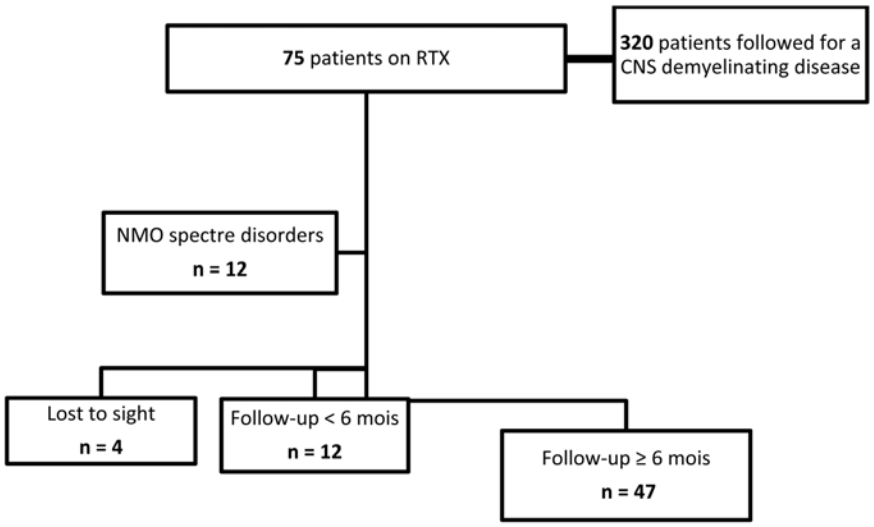

Figure 1. Patient inclusion.

Table 1. Socio-demographic and clinical characteristics of the patient.

Socio-demographic and clinical characteristics	
average age	39 ± 12 years
Female	61.7% (n = 29)
The duration of disease (mean)	8 ± 5 years
RRMS	83% (n = 39)
EDSS median at baseline	5.5
The annualized relapse rate (ARR)	0.8

Table 2. Reasons for rituximab initiation.

Reasons for Rituximab initiation	MS n (%)
Lack of efficacy with previous treatment	24 (51.10%)
Treatment naïve with active disease	16 (34 %)
Side effects from previous treatment	5 (10.60%)
Planning for pregnancy	1 (2.10%)
poor compliance with previous treatment	1 (2.10%)

(51%), and active disease in 16 patients (34%). RTX was proposed in 5 patients (10.6%) for intolerance to previous treatment (3 had an intolerance to cyclophosphamide and 2 to azathioprine).

The mean duration of RTX treatment was 21.8 ± 14.3 months. The ARR decreased from 0.8 to 0.2 after RTX initiation. 83% (n = 37) were relapse-free, in 5 patients (10.6%) had a single relapse, and 6.4% (n = 3) had 2 relapses.

During the observation time, the median EDSS remained unchanged at 70.2% (n = 33), and there was an improvement at 21.4% (n = 11). Progression was

noted in 6.4% (n = 3), of which 2 developed a secondarily progressive form and one refused to take her treatment during the COVID-19 pandemic.

The mean time for the baseline MRI was 4 ± 2 months. The average time for the control MRI was 16 ± 3 months. 78.7% (n = 37) had at least one control MRI, of which 83.7% (n = 30) had a stable MRI with no new lesions. 13.5% (n = 5) had a single new T2 lesion, and 5.4% (n = 2) had 2 new T2 lesions. Contrast enhancing lesions were absent in all patients who had an MRI with an injected T1 sequence (n = 25).

The side effects observed during the infusion were reported at 27.6% (n = 13). All these SEs were classified as grades 1 and 2 and no serious incident of hypersensitivity was recorded. For this side effect, the flow rate of the infusion was reduced and we did not stop completely the treatment.

Infections were observed in 19% (n = 9): All these infections were upper respiratory infections or lower urinary tract infections classified as grade 1 or grade 2.

Abortion was at 10 weeks of amenorrhea in one patient whose pregnancy occurred at 20 weeks from the last RTX infusion.

No cancerous or autoimmune complications have been reported so far.

4. Discussion

RTX is a chimeric anti-CD20 monoclonal antibody that was developed in the 1990s as a treatment for B-cell non-Hodgkin lymphomas [2]. Over time, this indication has been extended to other autoimmune diseases such as rheumatoid arthritis and Gougerot-Sjogren syndrome [2] [5]. Several recent studies have also suggested the effectiveness of RTX in some peripheral and central inflammatory neurological diseases, in particular MS [4] [5] [6] [7].

RTX binding to the CD20 causes depletion of CD20-expressing B-cells and T-cells. A depletion of autoreactive B cells will interfere with cell-mediated antigen presentation and impair T cell activation, antibody production, and cytokine secretion [2]. RTX works through three main mechanisms: induction of apoptosis, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity [2] [4] [5] [6].

CD20 is a very specific marker of B cells from the pre-B stage and on mature B cells, but it is not expressed on hematopoietic stem cells, or on the earliest precursors of the B line, or on plasma cells, thus making it possible to explain the transient nature of the depletion of B cells and the normal level of immunoglobulins in treated patients, which explains its acceptable safety profile [4].

It has been described that a subset of T cells also express CD20 and therefore their depletion may contribute to the therapeutic effect of RTX [2] [5].

A randomized, double-blind, phase II controlled study of RTX against placebo, over 48 weeks, including 104 patients with RRMS (HERMES study), proved its clinical and radiological efficacy with an acceptable safety profile [6]. The randomized phase III trial (OLYMPUS) of RTX, involving 439 patients with

primary progressive MS was negative, but the analysis of the subgroups showed a significant slowing of the progression of the disability in young patients (age < 51 years) with gadolinium-enhancing lesions on MRI [7].

In a review of the literature of 38 studies concerning the off-label use of RTX in RRMS, RTX appears to be effective in comparison to the placebo, IFNs, and glatiramer acetate [8] [9] [10]. A prospective phase III study (RIFUND-MS: NCT02746744) compares RTX to dimethyl fumarate in RRMS in Sweden, and the results are not yet been published of RTX.

Real-world data Off-label use of RTX in the treatment of MS is widespread throughout the world for its efficacy, its safety profile, and its easy administration [1] [2] [9]-[15], but protocols remain heterogeneous and uncodified.

We report our experience regarding the use of off-label RTX in Moroccan patients with MS with a mean treatment duration of 21.8 months. RTX has been used mainly as second-line therapy in patients with RRMS or in the case of first-line active forms. We observed a significant reduction in the ARR and the number of new lesions in the follow-up MRI after rituximab initiation.

The demographic data of our series are similar to the literature data concerning the population with MS. The diagnostic delay and the particular severity of MS in Moroccan patients may explain the high baseline EDSS in our series [16].

AEs during infusion are of variable severity, sometimes requiring treatment in an intensive care unit (18). Their incidence varies from 25% to 85% of cases [17]. This risk is more frequent when RTX is used in hematological malignancies than in autoimmune diseases [18] [19] [20].

Premedication, in particular glucocorticoid infusion, increases tolerance to first courses and reduces the risk of occurrence of serious AEs [2] [19] [20].

In our series, with compliance with premedication, no serious AEs during infusion were reported.

Data on the safety of RTX are reassuring based on the long-standing use of RTX in many diseases other than with low risks of serious opportunistic infections or malignancy [18] [19] [20].

The risk of serious infectious complications under RTX is explained by several hypotheses such as B cell depletion, hypogammaglobulinemia, and neutropenia [18] [19] [20] [21] [22].

It is important to note that the risk of infectious complications is also related to the indication of RTX, comorbidities, age, and association with other immunosuppressants. To minimize this risk, screen for hepatitis B and pulmonary tuberculosis, offer pneumococcal vaccination, and monitor white blood cells count and immunoglobulin levels before RTX infusion [21] [22].

A few rare cases of PML under RTX have been reported in other indications other than MS and it seems that the risk of PML is not related to the number of cures or the length of exposure to RTX [22] [23] [24] [25].

In our practice, hepatitis B serology as well as screening for pulmonary tuberculosis and serum protein electrophoresis is routinely done before initiating RTX. Pneumococcal vaccination should be done routinely but not necessarily

before initiation.

Data on the safety of RTX are reassuring based on the long-standing use of RTX in many diseases other than with low risks of serious opportunistic infections or malignancy [18] [19].

The risk of malignancy on RTX appears similar to that of the general population [18]. Our study has some limitations. First, the number of included patients is small. Second, our study was a retrospective longitudinal study.

5. Conclusions

Despite some methodological limitations, our work, like many series, confirms the efficacy and tolerance profile in MS and the easy administration of the treatment. From an economic point of view, it seems accessible compared to other long-term treatments.

So RTX represents an attractive therapeutic alternative, especially with resource-limited settings in developing countries like MOROCCO.

Conflicts of Interest

The authors declare that they have no competing interests.

Ethical Approval

The local ethic committee approved this study.

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Monkeypox in an Immunocompetent Vaccined Adult: A Case Report at the University Teaching Hospital of Bouake

Kone Djakaridja[1,2*], Yapo Martine Tatiana[1,2], Kadiane-Oussou Juliette[1,2], Akanji Iburaima Alamun[1], Gue Irené[2,3], Kouabenan Amon Stéphene[2,3], Koné Famoussa[2,4], Sule Mutiyu Akanbi[3], Kouamé Kouamé Gilles Renaud[2,4], Karidioula Jean Marie[1,2], Aba Yapo Thomas[1,2], Kra Ouffoue[1,2]

[1]Department of Infectious and Tropical Diseases, University Teaching Hospital of Bouaké, Bouaké, Ivory Coast
[2]Department of Medicine, Alassane Ouattara University (Bouaké), Bouaké, Ivory Coast
[3]Dermatology Department, University Teaching Hospital of Bouaké, Bouaké, Ivory Coast
[4]Internal Medicine Department, University Teaching Hospital of Bouaké, Bouaké, Ivory Coast
Email: *konedjakaridja18@gmail.com, tatianayapo@yahoo.fr, kadianeoussou14@gmail.com, iburaima@yahoo.com, minkpi01@gmail.com, stephandy2016@gmail.com, famousskone@gmail.com, masule541@gmail.com, kgilles22@gmail.com, jmkcyclase@yahoo.fr, chefaba@yahoo.fr, ouffouek@yahoo.com

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Abstract

Introduction: With the eradication of smallpox in 1980, vaccination against smallpox ceased and there was an upsurge in cases of monkeypox. The objective of this observation is to describe the characteristics of monkeypox in the vaccinated subject. **Case Report**: A 45-year-old, heterosexual, rural resident was referred for a rash. The history of the disease revealed signs of acute course marked by headache, asthenia, diffuse myalgia, chest pain, fever and pruritic rash. His background is marked by vaccination against smallpox in 1977, cohabitation with game hunters and domestic animals as well as a notion of contact with a person who presented similar but more generalized signs. The physical examination revealed a conscious patient with good general state, feverish, tachycardic, eupneic presenting skin lesions in the type of striated vesicles more or less umbilical, on the scalp, face, neck, trunk and the upper limbs associated with cervical lymphadenopathy. RT-PCR was performed on a dry swab by rubbing several vesicles and a throat swab proved positive for Monkeypox Virus (MPXV). Management consisted of isolation and symptomatic treatment. The evolution has been favorable. **Conclusion**: The symptomatology of monkeypox is similar to that of smallpox. Without widely available treatment or prophylaxis, rapid identification of cases is essential. Vaccination of people at risk is an alternative to curb the epidemic. However, the main prevention strategy is to raise awareness of the risk factors.

Keywords

Monkeypox, Rash, Immunocompetent, Bouaké

1. Introduction

Monkeypox (MPX) is an emerging zoonosis caused by monkeypox virus (MPXV), a member of the genus Orthopoxvirus in the family Poxviridae. It is one of four species of orthopoxviruses pathogenic for humans, together with variola virus, the causative agent of smallpox, now eradicated [1]. The Monkeypox virus was first isolated and identified in 1958 when monkeys shipped (hence the name) from Singapore to a research center in Denmark fell ill [2]. However, the first confirmed human case was in 1970 when the virus was isolated from a child in the Democratic Republic of Congo suspected of having smallpox [3]. Transmission can occur through contact with bodily fluids, skin lesions, or respiratory droplets of infected animals directly or indirectly via contaminated fomites. Although human-to-human transmission has previously been limited, mathematical modeling in the context of declining herd immunity to orthopoxviruses reflects a growing threat of disease spread between humans [4]. The disease usually begins with fever, followed by the development of multiple papular, vesiculopustular, and ulcerative lesions on the face and body and prominent lymphadenopathy [5]. Complications include pneumonitis, encephalitis, keratitis, and secondary bacterial infections [5]. The precise prevalence and incidence of Monkeypox are difficult to establish given the alleged gaps in disease reporting and confirmation. However, both parameters have increased since discontinuation of routine smallpox vaccination [6] [7]. In September 2017, monkeypox reappeared after a 39-year hiatus [8]. Monkeypox outbreaks are rarely reported, poorly managed and poorly described, giving an incomplete picture of the importance of the disease [6]. Also, since most cases of monkeypox are localized to Africa and rural areas, assumed underreporting may result in underestimating the potential threat of this pathogen [6]. Since early May 2022, there has been an emergence of monkeypox cases in more than 50 countries across five regions, prompting the World Health Organization on June 23, 2022, to declare monkeypox a public health emergency of international scope [9]. As of August 12, 2022, 31,799 cases have been reported worldwide, including 12 deaths [10]. In the same period, 383 cases were reported in Africa, including 7 deaths. This outbreak marks the first time monkeypox has spread widely outside of West and Central Africa. To date, no cases have been reported in Côte d'Ivoire [10]. Coincident immunity to monkeypox virus was previously achieved with vaccinia vaccination. However, the eradication of smallpox and the resulting lack of vaccination efforts paved the way for monkeypox [11]. We present a case of a non-severe form of monkeypox, in a contact person, immunocompetent and vaccinated against smallpox. The objective is to describe the characteristics of the disease in the vacci-

nated subject.

2. Case Report

He is a 45-year-old, heterosexual, rural resident, referred for a rash. The history of the disease revealed signs evolving 3 days before his admission marked by headaches, asthenia, diffuse myalgia, chest pain evolving in a context of unquantified fever. These signs led him to consult a primary health center where he was treated for simple malaria in the face of a positive rapid diagnostic test for falciparum. The evolution was marked 2 days later by the persistence of the signs and the appearance of pruritic vesicles sitting on the head, neck, trunk and upper limbs, which motivated the referral to the infectious diseases department. His background is marked by vaccination against smallpox, cohabitation with game hunters and domestic animals. There was no recent consumption of bushmeat or taking medication. In addition, we note 15 days before the onset of the signs, a notion of contact with a person who presented similar but more generalized signs, in whom the monkeypox virus was found on RT-PCR on a dry swab of the cutaneous vesicular fluid. Physical examination revealed a conscious patient in good general condition, feverish (39˚C), tachycardic (108 bpm), eupneic (17 cpm). The mucocutaneous examination revealed more or less umbilical striated vesicular lesions on the scalp, face, neck, trunk and upper limbs (**Figure 1**). There were no lesions in the conjunctival, oral, genital and anal mucosa. Hair and fingernails were normal. The spleno-nodal examination revealed polyadenopathies under the chin, bilateral laterocervical, occipital (**Figure 2**), which were painless, firm mobile with respect to the deep and superficial plane. No splenomegaly was noted. Faced with this clinical picture, the hypotheses of eruptive fever, namely, chicken pox, monkey pox or an insect bite were issued. Complete blood count and C-reactive protein assay were normal. The RT-PCR performed on a dry swab by rubbing several vesicles and the throat swab proved positive for Monkeypox Virus (MPXV) (**Figure 3**), confirming the diagnosis of

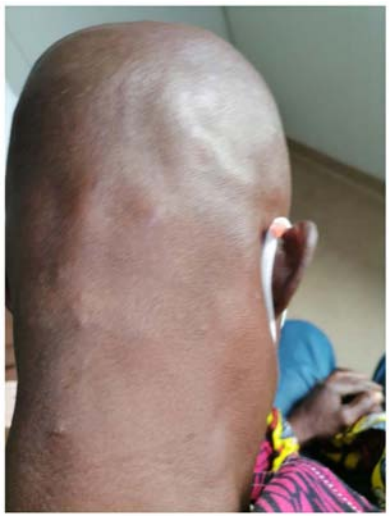

Figure 1. Umbilical blister lesions in a 45-year-old subject vaccinated against smallpox.

Figure 2. Cervical lymph nodes in a 45-year-old subject.

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Bouaké le : 12/08/2022

Laboratoire de Bactériologie - Virologie
Tel : 31000611

EXAMEN DE DISPOSITIF MEDICAL

N° de référence : **15MP2022**
N° du dossier :
Nom et Prénoms :
Age : 45 ans Sexe : Masculin
Service : SMIT BOUAKE
Prescripteur : Dr KONE Djakaridja
Renseignement clinque : éruption cutanée fébrile
Date de réception : 09/08/2022

Type d'examen : RT-PCR VIRUS DU MONKEYPOX (MPXV)
Type d'échantillon :
1) écouvillonnage naso-pharyngé
Résultat :

2) écouvillonnage de lésions cutanées
Résultat : **POSITIF**

Le biologiste

Figure 3. Monkeypox RT-PCR results.

monkeypox. Management consisted of isolation of the patient with oral feeding, administration of analgesic, antipyretic (paracetamol), antiasthenic (calcium ascorbate) and twice daily monitoring of haemodynamic constants (state of consciousness, temperature, blood pressure), and treatment of skin lesions with antiseptics and aqueous eosin. The evolution was favourable marked by the healing of the lesions and the formation of crusts (**Figure 4**).

3. Discussion

MPX has always been considered a rare sporadic disease with limited ability to spread between humans [12]. The clinical picture closely resembles that of smallpox, but the main difference that distinguishes MPX from smallpox is the enlarged lymph nodes that occur early, often at the onset of fever. A rash usually appears 1 to 3 days after the onset of fever and lymphadenopathy, with the lesions appearing simultaneously and progressing at a similar rate. Their distribution is mainly peripheral but can cover the whole body in severe disease [8] [13]. Internationally accepted case definitions recently expanded to include gay or bisexual men and other men who have sex with men as a risk group [14]. However in this reported case the patient was heterosexual. Other people most at risk are those who live or have close contact with someone who has monkeypox, or who have regular contact with animals that might be infected. The risk factors identified in this reported case were cohabitation with hunters and domestic animals that are susceptible to infection. Also, contact with someone with similar severe signs. Previous data noted that the rate of people living with an infected person and developing symptoms of MPXV infection ranged from 3% to 11% [15]. Previous reports have shown up to 6 events of intrafamilial transmission [16]. Transmission is thought to occur by means of salivary or respiratory droplets or

Figure 4. Disseminated hypochromic macules in a 45-year-old subject vaccinated against smallpox.

by contact with exudate from the lesion [17]. However, evidence suggests that infection can occur by direct inoculation [18]. Patient care consisted of isolation and symptomatic treatment. There is currently no specific treatment for monkeypox virus infection. As with most viral illnesses, patients are managed symptomatically [19]. For severe monkeypox virus infections, investigational antiviral therapies, such as tecovimat, cidofovir, or brincidofovir may be considered [20]. No complication was noted in this observation and the evolution was favorable. In the literature, few patients with Monkeypox have a serious illness requiring hospitalization. However, some patients may suffer from a variety of complications, including secondary bacterial infections, respiratory distress, bronchopneumonia, gastrointestinal involvement, dehydration, sepsis, encephalitis, and corneal infection with subsequent loss of vision [19]. The absence of complications could be explained by the fact that the patient was vaccinated against smallpox, which protected him against a severe form of the disease. Indeed, the existing vaccination against smallpox is 85% cross-effective against Monkeypox. 40 years ago it was estimated that 80% of the population was immune to smallpox, currently it is considered that this protection is around 30% [21]. This vaccination provides cross-protection against monkeypox or a very mild form of the disease [Harris E 2022]. There is currently a 3rd generation smallpox vaccine MVA-BN (Modified Vaccinia Ankara from Bavarian Nordic (en) (IMVANEX in Europe, JYNNEOS in the United States or IMVAMUNE in Canada), effective against monkeypox [22]. Identifying the potential benefits and harms of preventive vaccination against monkeypox in endemic communities requires further data collection and feasibility analysis [23]. Access to medical care, testing capacity and infrastructure limits the ability to make informed decisions about how best to treat this neglected tropical disease [19]. The main prevention strategy for monkeypox is to raise awareness of the risk factors and educate people about steps to take to reduce exposure to the virus. Also surveillance and rapid identification of new cases are crucial to containing outbreaks.

4. Conclusion

Monkeypox occurs mainly in the jungles of central and western Africa. The disease, unlike smallpox, is a typical zoonosis in that most cases occur following direct contact with an infected animal. However, human-to-human transmission is possible. Symptoms of the disease in humans can be very similar to those of smallpox, chickenpox, or other causes of vesiculopustular rash. Clinicians should be alert to unusual rashes. Without widely available treatment or prophylaxis, rapid identification of cases is essential. Vaccination of people at risk is an alternative to curb the epidemic. However, the main prevention strategy is to raise awareness of the risk factors.

Ethical Consideration

Patient gave his consent for the writing and publication of the study.

Contribution of the Authors

All the authors participated intellectually in the preparation and revision of the manuscript before its submission.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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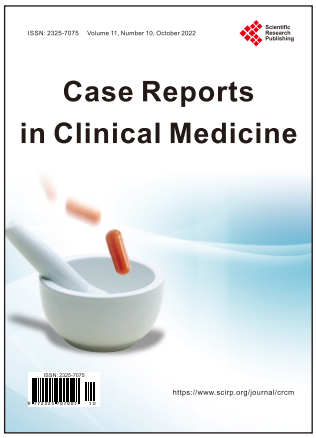

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