

Death of a steroid-dependent nephrotic syndrome patient taking levamisole: A case report

Case Report

Mahboubeh Neamatshahi (MD)¹

Elham Navipour (MSc)²

Zahra Barabadi (PhD)³

Aghil Keykhosravi (MD)^{4*}

1. Department of Community Medicine,
Faculty of Medicine, Sabzevar University of
Medical Sciences, Sabzevar, Iran.

ORCID ID orcid.org/0000-0001-5962-9442

2. Department of Anesthesiology, Faculty of
Paramedicine, Sabzevar University of
Medical Sciences, Sabzevar, Iran.

3. Department of Tissue Engineering, School
of Medicine, Hamadan University of
Medical Sciences, Hamadan, Iran.

4. Department of Pediatrics, Faculty of
Medicine, Sabzevar University of Medical
Sciences, Sabzevar, Iran.

ORCID ID orcid.org/0000-0003-2593-2448

* Correspondence:

Aghilallah Keykhosravi (MD), School of
Medicine, Department of Pediatrics,
University Pardis Building, Tohid Shahr
Blvd, Sabzevar, Khorasan Razavi
Province, 9613873136, I.R. Iran.

E-mail: drakeykhosravi@yahoo.com

Tel: +98 5144018440

Fax: +98 5144018440

Received: 11 June 2020

Revised: 28 Aug 2020

Accepted: 15 Sep 2020

Abstract

Background: Levamisole is an anthelmintic drug used in the treatment of patients with a diagnosis of steroid-dependent nephrotic syndrome. Skin rash has been reported as a drug side effect, but adverse events are really rare.

Case report: The case presented in this article was a 14-year-old boy with steroid-dependent nephrotic syndrome, treated with levamisole due to frequent relapse. He was admitted with rash, weakness, fatigue, fever, and weight loss. Levamisole was discontinued, and the patient's condition improved in the following two weeks. One year later, the nephrotic syndrome relapsed, and he received prednisolone and levamisole. He was admitted to the hospital six months after re-administration of these drugs because of vasculopathy, and unfortunately, he died due to disseminated intravascular coagulation (DIC).

Conclusions: Although levamisole is a suitable and cost-effective therapy for remission maintenance in steroid-dependent nephrotic syndrome, it is highly recommended to discontinue the drug without re-administration in case of reoccurring adverse effects, especially skin rash and systemic reaction, in addition to close monitoring of the patients under treatment.

Key Words: Child, Levamisole, Nephrotic Syndrome, Rash, Vasculopathy

Citation:

Neamatshahi M, Navipour E, Barabadi Z, Keykhosravi A. Death of a steroid-dependent nephrotic syndrome patient taking levamisole: A case report. *Caspian J Pediatr Sep 2020; 6(2): 430-33.*

Introduction

Nephrotic syndrome (NS) is a kidney disorder caused by damage to blood vessels in the kidneys which results in proteinuria and hypoalbuminemia. Nephrotic syndrome has relapsing and remitting periods in the majority of cases as well as it may cause serious complications such as anemia, heart attack, stroke, high blood pressure, cholesterol, and may result in acute renal failure and end-stage renal disease [1]. The symptoms include swelling (edema) especially in the feet and ankles. The steroid-sensitive type is one of the most common glomerular diseases in pediatrics. Steroids are the main treatment for this disorder in children, and additional treatments including diuretics, antibiotics, and dietary changes may be used to manage other symptoms. Steroid use in repeated courses induces steroid toxicity, so to reduce the relapse periods, several drugs have been suggested; for example, cyclophosphamide, cyclosporine and levamisole [2]. Levamisole is an anthelmintic drug with known immunomodulatory effects in steroid-dependent nephrotic syndrome (SDNS) [3], which is frequently used in patients with steroid-dependent nephrotic syndrome as it is cost-efficient and less toxic. Levamisole effectiveness has been proven in extending the duration of remission and decreasing the steroid dose in children with SDNS. Despite these benefits, vasculopathy has

been reported as a side effect, but this adverse event is rare. The role of levamisole in medical setting was reduced due to vasculopathy associated with autoantibodies such as p-ANCA, ANA and lupus anticoagulant [4].

The aim of this study was to report a single-center experience of a patient's death due to vasculopathy following the use of levamisole in the treatment of SDNS.

Case Report

The patient was a 14-year-old male diagnosed with pediatric steroid-dependent nephrotic syndrome (SDNS) (Image 1). He was first diagnosed at the age of 12. At the time of admission to the hospital, he was on prednisolone and levamisole for about six months, and he had generalized skin rashes on the anterior and posterior trunk and legs and suffered from weakness, fatigue, fever and weight loss. The laboratory findings included: WBC: 3200, PMN: 35%, CRP: 2+, BUN: 22, Cr: 0.7. In addition, C3, C4, CH50, and S/E were normal. Proteinuria, ANA, ds DNA and PANCA-CANCA were reported to be negative. The chest X-ray was also normal. An ultrasound imaging was performed, and accordingly, the kidneys' size, bladder, and urinary tract were normal. Levamisole was discontinued due to complications, and the patient recovered two weeks afterward.

However, because of relapse in the following year, the drug regimen including levamisole 2.5 mg per kg on alternate days [1] and prednisolone 5 mg daily was started again. However, six months later, the patient was referred to the hospital and admitted to the intensive care unit (ICU) due to the severe side effects of levamisole such as high fever, rash, myalgia, malaise, and tachypnea. He was critically ill. History and physical examination showed no sign of infection. Lab findings indicated leukopenia, anemia, neutropenia, thrombocytopenia, increased erythrocyte sedimentation rate and an elevated C-reactive protein (CRP) level. Bone marrow aspiration was not performed due to the patient's acute condition. Levamisole was stopped, and the patient received a stat dose of methylprednisolone 30 mg/kg on admission followed by a lower maintenance dose of 2 mg/kg prednisolone, cyclophosphamide and supportive care, thereafter. There was no improvement, and on the second day, the patient had respiratory distress with arterial blood gas (ABG) indicating respiratory acidosis. Hence, the patient got endotracheal intubated

and was placed on mechanical ventilation. He also received platelet and packed cells due to the anemia and thrombocytopenia. Unfortunately, he developed hemoptysis and died one week later due to disseminated intravascular coagulation (DIC).



Figure 1. Skin rash in the patient diagnosed with steroid-dependent pediatric nephrotic syndrome (SDNS).

Discussion

Levamisole is an anthelmintic agent with immunomodulatory effects. Its role in medical setting diminished in 1999 due to associated levamisole induced vasculopathy (LIV), agranulocytosis, thrombocytopenia and arthritis [4]. Sometimes, the LIV is associated with the production of autoantibodies including p-ANCA, ANA and lupus anticoagulant [4]. In the present study, these factors were reported to be negative before and after the levamisole consumption. This mismatch might be due to the fact that there is no exact mechanism known for levamisole induced vasculopathy [2].

Despite the beneficial role of levamisole in the remission maintenance of SDNS, patients on long-term treatment with levamisole should regularly be monitored clinically considering laboratory results with regards to complications such as vasculopathy [5].

Despite all the evidence on the side effects of levamisole, there is currently no efficient treatment for these complications. Although anticoagulants are a suggested option for the management of the adverse effects, the effectiveness of this therapy has not been proven [6].

It has been assumed that levamisole develops the Th1 lymphocyte-mediated immunity and suppresses

the Th2 lymphocyte-mediated immune response via selective transcription of several genes like interleukin 18 gene [6]. Recently, the levamisole's mechanism of action has been attributed to its direct effects on podocytes [7]. In the current study, the side effects of levamisole, especially in the first period of treatment, were eliminated by drug discontinuation and supportive care without the use of anticoagulants.

In a study conducted by Kuźma-Mroczkowska et al, the effectiveness of levamisole on the remission maintenance in children with frequent relapse nephrotic syndrome (FRNS) has been claimed [7].

Asymptomatic and reversible neutropenia has been reported in 14% of a study subjects (3 mild and 4 moderate cases) under treatment with levamisole as well as in one patient (severe) in the long-term follow-up phase in a randomized clinical trial [8]. As in the ongoing study, neutropenia was present for a long time following the use of levamisole. In the present study, in both phases of levamisole consumption, neutropenia was reported.

The findings of another study showed that levamisole was more effective in steroid-sensitive nephrotic syndrome rather than in steroid-resistant nephrotic syndrome. Two cases with side effects were reported in this study including granulocytopenia and a severe psoriasis-like cutaneous reaction; both were reversible after discontinuation of levamisole [9]. However, the most common skin manifestation due to the levamisole in this patient was petechiae and purpura.

Remission with no major adverse events was the findings of a study by Abeyagunawardena AS et al. in SDNS patients taking daily levamisole, and they believed that it is a suitable medication for the treatment of children with SDNS. Many studies have reported complete recovery with no severe side effects such as neutropenia and vasculopathy [10]. However, in our presented case, the re-administration of levamisole led to severe vasculopathy and eventually death.

One of the limitations of this study was not being able to perform a biopsy to determine the major cause of death.

In conclusion, although levamisole is a suitable and cost-effective therapy for remission maintenance in steroid-dependent nephrotic syndrome, it is highly recommended to discontinue the drug without re-administration in case of reoccurring adverse events, especially skin rash and systemic reaction. The patients should also be closely monitored for any symptoms.

Acknowledgement

This study is supported by a grant from the Sabzevar University of Medical Sciences. We would like to thank the Clinical Research Development Unit of Heshmatie Hospital, affiliated with the Sabzevar University of Medical Sciences for their assistance in this research.

Funding: None.

Ethical approval: This study obtained ethics committee of Sabzevar University of Medical Sciences (IR.MEDSAB.REC.1399.090).

Conflict of interest: There was no conflict of interest.

References

1. Mühlig AK, Lee JY, Kemper MJ, et al. Levamisole in children with idiopathic nephrotic syndrome: clinical efficacy and pathophysiological aspects. *J Clin Med* 2019; 8(6):860.
2. Levamisole for nephrotic syndrome 2014. Available from: <https://www.medicinesforchildren.org.uk/levamisole-nephrotic-syndrome>.
3. Madani A, Esfahani S, Rahimzadeh N, et al. Effect of levamisole in steroid-dependent nephrotic syndrome. *Iran J Kid Dis* 2010; 4(4): 292.
4. Sayadi L, Laub D. Levamisole-induced vasculitis. *Eplasty* 2018; 18.
5. Aoun B, Alali M, Degheili JA, et al. Distinctive vasculopathy with systemic involvement due to levamisole long-term therapy: a case report. *J Med Case Rep* 2018; 12(1): 209.
6. Lee G, Negash D, Arseneau R. Chronic levamisole-induced vasculitis: a case report. *BC Med J* 2012; 54(6): 302-3.
7. Kuźma-Mroczkowska E, Skrzypczyk P, Pańczyk-Tomaszewska M. Levamisole therapy in children with frequently relapsing and steroid-dependent nephrotic syndrome: a single-center experience. *Central-Europ J Immunol* 2016; 41(3): 243.
8. Gruppen MP, Bouts AH, Jansen-van der Weide MC, et al. A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. *Kid Inter* 2018; 93(2): 510-8.

9. Tenbrock K, Müller-Berghaus J, Fuchshuber A, et al. Levamisole treatment in steroid-sensitive and steroid-resistant nephrotic syndrome. *Pediatr Nephrol* 1998; 12(6): 459-62.
10. Abeyagunawardena AS, Karunadasa U, Jayaweera H, et al. Efficacy of higher-dose levamisole in maintaining remission in steroid-dependant nephrotic syndrome. *Pediatr Nephrol* 2017; 32(8): 1363-7.