Potential role of thalidomide in the management of chronic pelvic pain. Cases report

Papel potencial da talidomida no tratamento de dor pélvica crônica. Relato de casos

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ABSTRACT

BACKGROUND AND OBJECTIVES: Chronic pelvic pain is a condition that lacks specific treatment and often is refractory to several therapeutic approaches. This study aims to report two patients in whom chronic pelvic pain was nearly completely controlled with thalidomide as an add-on therapy.

CASES REPORT: The response to therapy of two postmenopausal women who presented to our service with a longstanding history of refractory chronic pelvic pain secondary to interstitial cystitis is reported. Due to their uncontrolled pain and consequent poor quality of life, these women were started on thalidomide at 25 mg/day as an add-on therapy. At one-month follow-up, the patients' pain was reduced in 80% and 70%, respectively. Subsequently, their pain increased, but was again relieved with higher doses of thalidomide. Notably, this medication was well tolerated by both patients. At one-year follow-up and eleven-month follow-up (respectively), their pain has remained controlled and their quality of life is significantly improved.

CONCLUSIONS: These results suggest that thalidomide may have therapeutic value for chronic pelvic pain/interstitial cystitis. Based on previously published data, we hypothesize that suppression of TNF-alpha may be one of the mechanisms by which thalidomide controls pelvic pain. Our study may lead to a better understanding of the currently unclear pathogenesis of chronic pelvic pain. Lastly, we hope to encourage further studies to establish the efficacy and safety of thalidomide for CPP and other chronic pain conditions.

Keywords: Chronic pelvic pain, Interstitial cystitis, Refractory Pain, Thalidomide.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A dor pélvica crônica é uma condição que não possui tratamento específico e é geralmente refratária a várias formas terapêuticas. Este estudo teve como objetivo relatar duas pacientes nas quais a dor pélvica crônica foi praticamente controlada com a talidomida como terapia complementar.

RELATO DOS CASOS: Resposta à terapia de duas pacientes no período de pós-menopausa que compareceram ao nosso serviço com um longo histórico de dor pélvica crônica refratária, secundária a cistite intersticial. Como terapia complementar foi iniciada talidomida (25mg/dia), devido à dor sem resposta ao tratamento. No seguimento após um mês, a dor das pacientes havia reduzido em 80 e 70%, respectivamente. Posteriormente, a dor aumentou, sendo controlada com doses mais altas de talidomida. O fármaco foi bem tolerado por ambas as pacientes. No seguimento de um ano e 11 meses, respectivamente, a dor permanecia controlada.

CONCLUSÃO: Os resultados sugerem que a talidomida pode ter valor terapêutico para dor pélvica crônica relacionada a cistite intersticial. Baseados em dados já publicados, levantou-se a hipótese de que a supressão de TNF-alfa possa ser o principal mecanismo pelo qual a talidomida controla a dor pélvica.

Descritores: Cistite intersticial, Dor pélvica crônica, Dor refratária, Talidomida.

INTRODUCTION

Thalidomide was developed in 1953 as a sedative. Soon after, it was found to be analgesic and also effective in treating morning sickness of pregnancy. Its use in pregnancy resulted in the tragic figure of 8,000 children with congenital malformations, leading to the virtually complete withdrawal of this drug from clinical practice. Currently, thalidomide is used as an immunomodulatory and anti-inflammatory drug, indicated for the treatment of multiple conditions including Crohn's disease and Behçet's disease[1].

Chronic pelvic pain (CPP) refers to pain of at least six months' duration that, by definition, is severe enough to cause functional impairment or to require treatment. Its prevalence is 3.8% in women ranging from 15 to 73 years of age. Concerning its pathophysiology, it has been hypothesized that noxious stimuli, secondary to tissue damage, increase the production of several components of the "inflammatory cascade" directly affecting nociceptors. One of these substances is known as a tumor necrosis

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factor alpha (TNF alpha), a cytokine that plays an active role in the process of neurogenic inflammation and perhaps in the chronicity of pain[2]. Treatment for CPP is known to be challenging, for which reason new therapies have been investigated – especially within the last few years.

Herein, we report two patients in whom CPP was nearly completely controlled with thalidomide. Thalidomide's known effects of decreasing TNF-alpha and interleukin-12[3] serum levels may be the responsible for the great symptomatic improvement observed in reported patients – raising the hypothesis that chronic inflammation plays a key role in the pathophysiology of CPP.

This study aimed at reporting the case of two patients in whom pelvic pain was virtually controlled with thalidomide as adjuvant therapy.

CASES REPORT

A 64-year-old woman (patient 1) presented to our hospital in February 2015 with a 16-year history of severe, refractory vulvar and perineal pain, which was continuous and worsened by sitting and voiding. This pain, which was described as burning and rated as 10/10 in intensity - per visual analogue scale (VAS), did not allow patient to sit down and was significantly affecting her quality of life. She had been previously diagnosed with interstitial cystitis thus submitted to multiple therapies. These included oral medications (amitriptyline, pregabalin, gabapentin, alprazolam, fluoxetine, citalopram, methadone and morphine) and surgical procedures – intradetrusor botulinum toxin injection, presacral neurectomy, and superior hypogastric plexus neurolysis – all of which failed to control her pain.

At presentation, she was using amitriptyline (50mg/day), gabapentin (1,800mg/day), citalopram (10mg/day), alprazolam (1mg/day) and methadone (5mg) every other day. Interestingly, she also reported a history of intermittent painful oral ulceration. Despite the absence of any constitutional symptom, eye lesions, skin lesions, or genital ulceration, a diagnosis of Bechet's disease was considered. Based on the exquisite, refractory pelvic pain in association with the history of painful oral ulcers, thalidomide (25mg/day) was added to her drug regimen. At follow-up, one month later, she reported impressive pain reduction (2/10, VAS) and improvement in being able to sit. At four-month follow-up, her pain increased to 6/10 (VAS) and she reported mild somnolence as the only side effect. Thalidomide dose was then escalated to 300 mg/day. Presently, at one-year follow-up, pain is rated as 4/10 (VAS) and no other side effects developed (Figure 1) Notably, her other medications (described above) remained unaltered throughout the treatment with thalidomide. Patient's satisfaction with treatment was assessed with the Pain Outcomes Questionnaire (POQ) and and Pain Treatment Satisfaction Scale (PTS)[4]; the score was 47/50.

Similarly, a 93-year-old woman (patient 2) presented to our hospital in March 2015. This woman complained of a 4-year history of severe, refractory vulvar and perineal pain, which was continuous and described as burning. Pain was rated as 10/10 (VAS) and interfering with her quality of life. She had also been diagnosed with interstitial cystitis, thus submitted to multiple medical therapies – including tramadol, gabapentin, clonazepam, and morphine – which failed to improve pain.

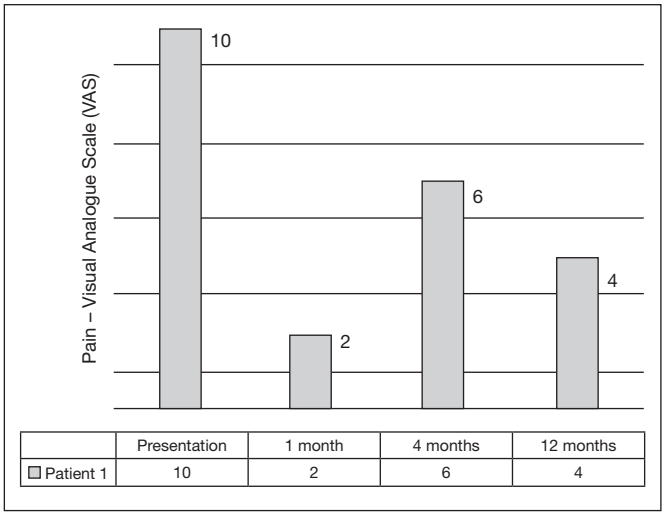

Figure 1. Patient reported pain scores based on visual analogue scale during the treatment with thalidomide (Patient 1)

At presentation, she was using gabapentin (300mg/day), clonazepam (0.5mg/day), trazodone (100mg/day), and morphine (5mg/day). Thalidomide at 25 mg per day was added to her drug regimen. At one-month follow-up, she rated pain as 3/10 (VAS) and stated significant improvement in her quality of life; no side effect was reported. At six-month follow-up, her pain score increased to 5/10 (VAS); therefore, thalidomide dose was increased to 50 mg qam and 100 mg qpm Presently, at 11-month follow-up, she reports full improvement of pain (0/0, VAS) and continues side effect-free. (Figure 2) Notably, her other medications, previously described, remained unaltered throughout the treatment with thalidomide. Patient's satisfaction with treatment was also assessed with the PTS[4]; the score was 48/50.

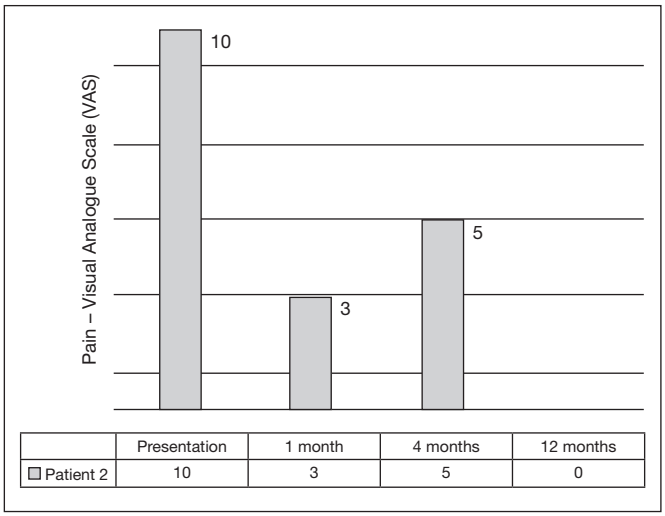

Figure 2. Patient reported pain scores based on visual analogue scale during the treatment with thalidomide (Patient 2)

DISCUSSION

Thalidomide was introduced in Europe as sedative and antiemetic in the late 1950s. Approximately a decade after, this drug was withdrawn from the market due to its linkage to teratogenesis. In the last couple of decades, however, thalidomide has reemerged – mostly because of its analgesic, anti-inflammatory, immunomodulatory, and antiangiogenic properties[3,5]. Based on these features, thalidomide has been used for the treatment of several conditions ranging from autoimmune disorders (e.g. Crohn's disease and rheumatoid arthritis), skin diseases (e.g. chronic pruritus, lepromatous leprosy, cutaneous lupus, Behçet syndrome), neoplastic diseases (e.g. multiple myeloma and melanoma), chronic pain/inflammatory conditions (e.g. complex regional pain syndrome and radiculopathic pain)[6]. Particularly concerning its anti-inflammatory and immunomodulatory capacities, thalidomide has been found to selectively reduce the synthesis and expression of tumor necrosis factor alpha (TNF-alpha). By suppressing TNF-alpha, there is a consequent decrease in various other pro-inflammatory cytokines, including interleukin 1Beta (IL-1B), interleukin 6 (IL-6) and interleukin 8 (IL-8), leading to an overall inhibition of inflammation[3].

Despite the rich literature on the use of thalidomide for the above-mentioned diseases, there is little data assessing this drug's activity in chronic pelvic pain (CPP). To our knowledge, only one clinical study has explored the effects of thalidomide in pelvic pain. This study involved ten patients with relapsing endometriosis treated with a combination of GnRH analogue and thalidomide followed by thalidomide alone. Interestingly, eight of the ten women remitted during the therapy with GnRH analogue plus thalidomide, with no relapse even when patients were solely on thalidomide[7]. The authors hypothesized that the symptom control observed in these patients was due to the antiangiogenic property of thalidomide. An experimental study originally reported inhibition of TNF-alpha-induced IL-8 production by thalidomide in human endometrial stromal cells[8]. More recently, thalidomide was evaluated in a rat model of endometriosis. This study showed that this drug was effective in treating endometriosis in rats based on pathological improvement as well as reduction in serum leukocytes and peritoneal IL-6 and VEGF[9]. These experimental findings, in conjunction with the pilot clinical study described[7], suggest that thalidomide might be, in fact, a promising therapy for endometriosis/chronic pelvic pain – through antiangiogenic and/or immunomodulatory and analgesic properties. However, both of our patients were already menopaused, a finding that extends thalidomide efficacy to causes of chronic pelvic pain other than endometriosis and probably not related to its anti-angiogenic effect.

Irrespective of the exact etiology, CPP represents a major challenge to health care providers, especially because of its common refractoriness to treatment. In this context, adding an effective and well-tolerated drug, as thalidomide, to our armamentarium of pain medications would be extremely valuable. Results presented herein – our two patients' impressive pain relief response to thalidomide – suggest that this drug may have therapeutic value for interstitial cystitis/CPP. Moreover, based on our results, we hypothesize that suppression of TNF-alpha (a proved effect of thalidomide) may contribute to pain relief in patients with CPP. This hypothesis may lead to a better understanding of the currently unclear pathogenesis of CPP. Finally, we hope to encourage further studies to establish the efficacy and safety of thalidomide for chronic pelvic pain and other chronic pain conditions.

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