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Morfeia e Terapia Hormonal: Uma Associação Possível

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RESUMO – A morfeia é uma doença inflamatória, rara, de etiologia desconhecida. Apresentamos o caso de uma mulher de 35 anos com áreas de espessamento cutâneo no tronco e membros, e artralgias inflamatórias, com 18 meses de evolução. Os sintomas começaram 2 semanas após um tratamento de fertilidade. O exame físico e exames complementares confirmaram o diagnóstico de morfeia, pelo que iniciou deflazacorte e metotrexato com melhoria significativa dos sintomas. Seis anos depois, a doente realizou um novo tratamento de fertilidade com agravamento da doença. A associação temporal entre os tratamentos de fertilidade e o início e agravamento da morfeia sugerem uma influência das hormonas sexuais na sua fisiopatologia.
PALAVRAS-CHAVE – Esclerodermia Localizada/etiologia; Esclerodermia Localizada/tratamento por fármacos; Hormonas/uso terapêutica; Infertilidade/tratamento.

Morphea and Hormonal Therapy: A Possible Association

ABSTRACT – *Morphea is a rare inflammatory disorder with an unknown etiology. We report the case of a 35-years-old woman presenting with an 18-month history of skin thickening on the extremities and trunk, and inflammatory arthralgia. Complaints started 2-weeks after a fertility treatment. The physical exam and workup confirmed the diagnosis of morphea, and the patient started treatment with deflazacort and methotrexate, with significant improvement. Six years later, the patient was submitted to another fertility treatment with exacerbation of the disease. The temporal association between the fertility treatments and the onset and further worsening of morphea suggest an influence of sex hormones on its pathophysiology.*
KEYWORDS – *Hormones/adverse effects; Hormones/therapeutic use; Infertility/therapy; Scleroderma, Localized/etiology; Scleroderma, Localized/drug therapy.*

INTRODUCTION

Morphea, also known as localized scleroderma, is a rare inflammatory disorder, which ultimately leads to skin sclerosis. Its etiology is not well understood, but genetics and environmental factors appear to contribute. Three major mechanisms are thought to involve sclerosis: vascular disruption, activated T cells and altered connective tissue production by fibroblasts.[1-3] Triggering events include mechanical trauma, injections, vaccinations and X-irradiation.[1] Except for linear morphea, the disease as a higher prevalence among women favoring a potential role of sex hormones as a triggering agent for this disease.[4] There are also reports of developing or worsening of morphea during pregnancy.[5,6]

Skin involvement is characterized by an early inflammatory and edematous stage, followed by sclerosis and subsequent atrophy. The disease activity usually stops after 3 to 6 years. In patients with deeper forms of morphea, contractures may develop. Despite being limited to the skin, in severe and deep forms, extra-cutaneous manifestations

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DOI: https://dx.doi.org/10.29021/spdv.78.1.1145

Recebido/*Received* 2019/12/10 | **Aceite/*Accepted*** 2020/03/10 | **Publicado/*Published*** 2020/04/--

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may occur and result in cosmetic mutilation and disability that persist after the resolution of disease activity.[7,8]

CASE REPORT

A 35-years-old woman, smoker, was admitted at the rheumatology department due to an 18-month history of several areas of skin thickening. She also had inflammatory arthralgia, morning stiffness around 2 hours and significant functional impairment, without any other systemic symptoms. These complaints started 2-weeks after a successful fertility treatment with an initial combination of follitropin beta and ganirelix (a GnRH antagonist), followed by human menopausal gonadotrophin, and 4 months later with a combination of human menopausal gonadotrophin and cetrotide. During pregnancy lesions slowly developed, and the complaints worsened after delivery. The patient denied other relevant exposure or family history of autoimmune diseases.

On physical examination, the patient had several large sclerotic hyperpigmented plaques on the extremities and trunk. Some lesions were associated with cutaneous atrophy and hypoesthesia (Figs. 1 a, b). There was left-hand flexor tenosynovitis, peripheral polyarthritis – involving right elbow and wrist; proximal interphalangeal (2nd to 5th on the right hand, and 2nd, 3rd and 5th on the left hand); and limited flexion of the left ankle joint due to skin thickening. There were no other relevant findings on physical examination.

The laboratory workup, which included a complete blood cell count, erythrocyte sedimentation rate, C-reactive protein (CRP), liver enzymes, creatinine, fasting glucose, and autoimmunity panel, showed CRP of 1.0 mg/dL (normal range <0.5 mg/dL), positive antinuclear antibodies (ANA) 1/160 and negative extractable nuclear antigens (ENA), without any further alterations. Nail fold capillaroscopy was normal. Skin biopsy was not performed.

Based on the clinical picture the diagnosis of morphea was assumed and treatment was started with deflazacort 6 mg/day (50 kg), methotrexate 15 mg/week (increased to 20 mg/week, and then switched to 15mg/week subcutaneous for gastrointestinal intolerance) and painkillers.

There was a significant improvement of pain and remitting of polyarthritis and flexor tenosynovitis, after more than 6 months of immunosuppressive treatment. In the subsequent year the methotrexate dose was progressively reduced and deflazacort was withdrawn. Skin lesions remained stable in size along the years, but skin sclerosis decreased progressively.

Six years later, the patient was submitted to another fertility treatment (human menopausal gonadotrophin and a GnRH antagonist), that was not successful, but induced exacerbation of the disease within 1-month, characterized by worsening of previous lesions and two new sclerodermatous lesions on the breasts, sparing the nipple (Fig. 1c). Treatment was again started with deflazacort 6 mg/day and oral methotrexate 10 mg/week, with good response.

DISCUSSION

Morphea affects both children and adults.[7] Pregnancy or other hormonal changes, like hormonal treatments, seem to predispose to this cutaneous disorder.[5,6,9,10,12] The responsible mechanism for hormonal-related morphea is unknown, but hormonal and immunological changes could contribute to this disorder.[10,11] Some clinical studies have shown, in menopausal women, the link between estrogen supplementation and skin thickening.[10,11] Furthermore, five cases of morphea that either developed or worsened during pregnancy were previously reported. In the reported cases, the proposed mechanism was microchimerism, a process where cells transferred from the fetus to the mother, promote the activation of immune system.[5,6,9,12,13]

In this case, morphea started just after the first successful fertility treatment and lesions worsened and new lesions developed after a second fertility treatment. However, to our knowledge, there are no published cases of morphea induced by drugs used for fertility treatments and

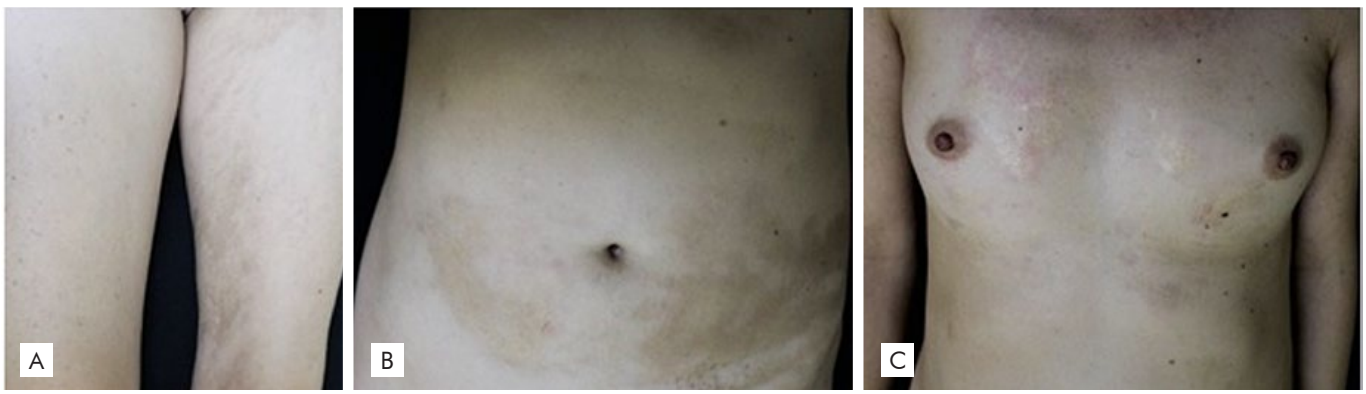

Figura 1 - (A, B) – Sclerodermatous lesions (linear and generalized) with cutaneous atrophy on the thigh and the abdominal left flank after first fertility treatment; (C) – Sclerodermatous lesions on the breasts that appeared only after second fertility treatment.

it is not a reported side effect of these drugs. Nevertheless, it is known that progesterone raises 17 b-estradiol levels, which, through its skin receptors, regulate fibroblast proliferation and tissue-degrading matrix metalloproteinase synthesis. Soldano *et al* demonstrated that estrogens stimulate the production of basic fibroblast growth factor and increase the secretion of the transforming growth factor (TGF-beta 1) in vitro. We hypothesized that higher levels of 17 b-estradiol induced by fertility treatment may be involved in promoting the cutaneous fibrotic process, as observed in this patient, but more studies need to be done.[10,11]

Regarding treatment several retrospective studies reported the use of methotrexate in morphea and its efficacy and safety have been reported in randomized control trials when used along with systemic steroids. Its antifibrotic effects was exerted via inhibition of inflammatory cytokines such as IL-2, IL-4, IL-6, IL-8, and TNF-alpha and adhesion molecules such as ICAM-1.[14,15]

The temporal association between the fertility treatments and the onset and further worsening of morphea reinforces its relationship. This case highlights the possible influence of sex hormones on the pathophysiology of morphea and the need to consider fertility drugs as a potential trigger to this disabling disease.

Conflitos de interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Consentimento: Consentimento do tutor legal para publicação obtido.
Proveniência e revisão por pares: Não comissionado; revisão externa por pares.

Conflicts of interest: *The authors have no conflicts of interest to declare.*
Financing support: *This work has not received any contribution, grant or scholarship.*
Confidentiality of data: *The authors declare that they have followed the protocols of their work center on the publication of data from patients.*
Patient Consent: *Consent for publication was obtained.*
Provenance and peer review: *Not commissioned; externally peer reviewed*

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