Primary anetoderma in a woman after ovarian stimulations for in vitro fertilization program

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Key words: anetoderma; drug induced; in vitro fertilization; ovarian stimulation.

INTRODUCTION

Anetoderma is an uncommon benign skin disorder characterized by diffuse flaccid or herniated sac-like skin, with or without inflammation. The histopathologic clue is represented by focal loss of dermal elastic tissue.[1] The disease is currently classified as primary or secondary. Primary forms usually present on normal-looking skin and are generally associated with autoimmune diseases or with ocular, bony, and cardiac abnormalities. They usually appear between ages 20 and 40 but may occur at any age, with a mild female predominance. Secondary anetoderma generally appears in areas of previous or concomitant infections and neoplastic or inflammatory dermatoses. Varicella, borreliosis, acne, mastocytosis, prurigo nodularis, nodular amyloidosis, generalized granuloma annulare, juvenile xanthogranuloma, pilomatricoma, plasmacytoma cutis, and B-cell lymphoma are among the associated skin disorders. Other rare forms of anetoderma include iatrogenic, observed in premature infants in areas in which monitoring electrodes are placed; congenital, manifesting on the trunk of premature infants at birth; familial; and drug induced by penicillamine.[2] The pathogenesis of anetoderma is still unknown. It is thought to reflect an imbalance of dermal elastin turnover, as evidenced by elevated levels of several members of the matrix metalloproteinases without an equivalent increase in their tissue inhibitors.[3] Other possible explanations for the loss of elastic tissue include defective elastin synthesis, uncontrolled production of elastolytic enzymes, elastophagocytosis, or degeneration of elastic fibers.[4,5] We report a case of primary anetoderma after ovarian stimulation for an in vitro fertilization (IVF) program.

Abbreviation used:
IVF: in vitro fertilization

CASE REPORT

A 37-year-old nulliparous woman was referred to our clinic for multiple flaccid papules located on her abdominal skin. Medical history was positive for, in the last 4 years, 4 (1 per year) ovarian stimulations for infertility treatment, consisting of subcutaneous hormonal injections in the abdominal area of 200 to 250 UI/d of recombinant follicle-stimulating hormone combined with 75 UI of luteotropin-α and gonadotropin-releasing hormone antagonist for 9 consecutive days, followed by 10,000 IU of human chorionic gonadotropin on the tenth day. After the first protocol, the patient reported the appearance of small self-limited erythematous patches at the injection sites. A few days after the last ovarian stimulation protocol in 2017, she noticed the appearance of atrophic lesions on the abdominal area. Physical examination found multiple asymptomatic red-rounded pearly white, atrophic, flaccid papules, ranging from 1 to 2 cm in diameter, partially coalescent, easily herniating into the skin upon palpation, located at injection sites and surrounding abdominal skin (Fig 1). Histologic examination from

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Funding sources: None.
Conflicts of interest: Dr Musumeci has received fees/honoraria from Eli Lilly, Janssen-Cilag, Biogen, and AbbVie. The rest of the authors have no conflicts to declare.

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JAAD Case Reports 2019;5:466-7.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.03.004

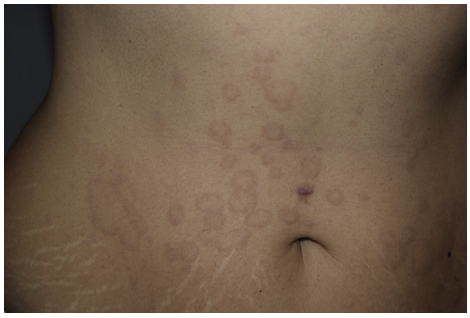

Fig 1. Red-rounded pearly white, atrophic, flaccid papules, partially coalescent, located on abdominal skin.

a 5-mm punch biopsy found slight perivascular lymphohistiocytic infiltrate, associated with fragmentation of the elastic fibers in the dermis, confirming the clinical suspicion of anetoderma. Laboratory tests found low level of serum hemoglobin, protein C3, iron, and ferritin; homocysteine serum levels were 20.66 μmol/L (normal range, 4-15 μmol/L). As requested by international protocols, before IVF, a genetic screening for heritable thrombophilia was performed. The patient was heterozygous for both the prothrombin gene *G20210A* variation and the methylenetetrahydrofolate reductase gene *C677T* mutation, the latter being responsible for hyperhomocysteinemia.

DISCUSSION

The epidemiology and natural history of anetoderma generally do not clearly support the hypothesis that it may be linked to female sex hormones, although primary anetoderma occurs slightly more frequently in women age 20 to 40 years. In our patient, its onset soon after a series of subcutaneous injections for IVF suggests that hormonal therapies may play a causative role by inducing a thrombotic effect. Her genetic profile was consistent with a prothrombotic state, as *G20210A* is recognized as a genetic cause of hypercoagulability along with increased levels of circulating prothrombin.[6] A possible association between primary anetoderma and a hypercoagulable state was suggested in a series of 9 patients, in which at least 1 prothrombotic abnormality was observed in each patient.[7] These abnormalities may be responsible for microthromboses of the dermal vessels with development of local ischemia leading to degeneration of elastic tissue.[7] The *C677T* gene mutation found in our patient is linked to increased plasma homocysteine. Hyperhomocysteinemia may predict and precede the occurrence of cardiovascular and thromboembolic diseases by inducing increased vascular thickness, collagen irregularities, and elastic fiber fragmentation in arteries. Elevated homocysteine associated with anetoderma in a young woman with a history of anorexia nervosa suggests that the inherited risk for thrombosis could play a pathogenic role in both diseases.[8] In a study evaluating the skin of patients with anorexia nervosa, the median collagen content was significantly reduced in the anorectic group (164 μg/mm^2) compared with the control group (209 μg/mm^2).[9] The risk for a thrombotic event in women of reproductive age undergoing IVF is estimated to be 10 times higher than that of women without infertility,[10] further supporting the connection between anetoderma and a prothrombotic state in our patient.

Our case suggests that women of reproductive age with thrombotic predisposition undergoing ovarian stimulation for IVF should be warned about the potential risk of anetoderma, although additional factors that may increase coagulability should be considered and evaluated.

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