LETTER TO THE EDITOR

A case of deep vein thrombosis in a young male treated with tamoxifen for idiopathic infertility

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Dear Editor,

We present here a case of idiopathic male infertility who developed deep vein thrombosis (DVT) with the use of tamoxifen, a selective estrogen receptor modulator, probably through a hypercoagulable state.

A selective estrogen receptor modulator (SERM) is a compound that can act as an estrogen agonist or antagonist, depending on the specific target tissue. At present, four SERMs are approved for clinical use: clomiphene, raloxifene, tamoxifen, and toremifene. In women, SERMs are widely used as adjuvant therapy for breast cancer. SERMs in males have been suggested as an empiric treatment for idiopathic infertility, but relatively few studies are currently available.1

Tamoxifen administration in males indirectly stimulates follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion by blocking estrogen receptors in the hypothalamus and pituitary gland, thus increasing the hypothalamic release of gonadotrophic releasing hormone (GnRH). The major effect of tamoxifen administration is the stimulation of Leydig cells to produce testosterone and of Sertoli cells to stimulate hormone (FSH) and luteinizing hormone (LH) secretion, increasing the hypothalamic release of gonadotrophic releasing hormone (GnRH). The major effect of tamoxifen administration is the stimulation of Leydig cells to produce testosterone and of Sertoli cells to stimulate hormone (FSH) and luteinizing hormone (LH) secretion, increasing the hypothalamic release of gonadotrophic releasing hormone (GnRH).

Noteworthy, tamoxifen, which is widely used as adjuvant therapy for breast cancer in women, increases the risk of thromboembolic events.4 To the best of our knowledge, no known clotting abnormalities in males treated with tamoxifen for idiopathic infertility have been reported, also because it is used as an off-label treatment and rigorous safety analyses are lacking.

Anticoagulant treatment with low-molecular-weight heparin (enoxaparin) was initiated along with warfarin for 5 days. After the therapeutic range was reached (i.e. prothrombin time 2–3 by international normalized ratio), treatment was continued with warfarin alone. On discharge, D-dimer levels were reduced (6.96 µg ml⁻¹) and Doppler ultrasonography of the deep venous iliac – femoral – popliteal system showed signs of initial recanalization and thrombus dissolution.

Among different treatments proposed for idiopathic male infertility, anti-estrogens, like tamoxifen, may be taken into account. Tamoxifen seems to have a positive effect on sperm count and concentration in eugonadal patients, but it does not improve other semen parameters such as motility, morphology, and viability probably due to its effects on the first steps of spermatogenesis.2 Literature data suggest a better effect of tamoxifen in patients with low FSH levels, suggesting the need for a well-functioning hypothalamic-pituitary-gonadal axis.

On the other hand, oxidative stress has well-recognized deleterious effects on sperm function. Estrogens have been shown to modulate the antioxidant system in human semen, and this provides a further rationale for antiestrogen administration in male infertility.7

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The potential mechanism for the procoagulant effect of tamoxifen has not been fully elucidated, although a reduction in antithrombin III and protein C levels or an APC resistance phenotype have been reported.9

We conclude that immobilization due to the recent long haul trips along with the use of tamoxifen-induced a hypercoagulable state, thus increasing the risk of thrombosis in this patient. We observed
an increase in factor VIII activity which favors the propagation and amplification, rather than the initiation, of the coagulation cascade, increasing the risk of venous thrombosis.\(^\text{10}\)

Although a single case in not sufficient to state a cause and effect relationship between tamoxifen and deep vein thrombosis, clinicians should be aware of the possibility of thromboembolic complications during tamoxifen treatment in males, even when it is administered for short periods of 3–6 months. Other treatments for idiopathic male infertility should be considered in male patients with an elevated risk of thromboembolism.

**AUTHOR CONTRIBUTIONS**

SA was the physician in charge of the patient described in the case study, drafted the manuscript and critical discussion; GM and MM participated in manuscript drafting and critical discussion; MPT participated in the critical discussion; FL participated in the critical discussion and revised the manuscript.

The authors have nothing to disclose about the data presented in this manuscript.

**COMPETING FINANCIAL INTERESTS**

We declare that we have no competing financial interests.

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