Progestins and the Onset of Cervical Vasculitis in a Patient with Ankylosing Spondylitis

Abstract

Background: The cervical vasculitis is rare and can appear on healthy subjects or on the background of another autoimmune disease. There is insufficient evidence for the role exogenous hormones might have in the acute onset of this condition.

Case report: A 27 year old nulliparous woman known having ankylosing spondylitis (AS) for the past eight years was seen as an emergency in gynecology ward with severe vaginal discharge and a necrotic inflamed cervix highly suspicious of malignancy. The histology of the loop excision of the transformation zone (LLETZ) specimen revealed acute vasculitis of the cervix. No cervical dysplasia was identified. There was no alteration in the medical history prior to this event apart from the recent change of contraception to injectable medroxyprogesterone (MPA) from combined oral contraceptive (COCP).

Conclusions: Isolated vasculitis of the genital tract is rare. The association with an autoimmune disease is possible. The progestins have complex modulator action on inflammation and autoimmunity, however, the link with this condition has not been mentioned in literature before.

Keywords: Cervical vasculitis; Progestin; Ankylosing spondylitis

Introduction

The cervical vasculitis is rare; can present associated with vaginal discharge or bleeding. However, it can be just an incidental finding after a surgical resection. To date, no studies have evaluated the generalised or localised vasculitis onset relationship with immune-endocrine changes associated with contraception intake [1].

The ankylosing spondylitis (AS) is a degenerative autoimmune disease with distinct prevalence and clinical characteristics between men and women with the hormonal profile of each sex being considered to play a role. The prevalence between genders after the discovery of human leukocyte antigen (HLA-B27) is of approximately 3-4:1 men to women [2]. The pathogenesis is not entirely understood. The immune-mediated mechanisms involving (HLA)-B27, inflammatory cellular infiltrates, cytokines (Tumour Necrosis Factor α-TNFα, Interleukin10-IL10) and genetic factors are considered to be strongly involved [3]. The decision for prescription of exogenous hormones in patients with autoimmune disease is primarily influenced by the risk of thrombosis, disease flare, neurovascular disorders (such as complicated migraines) and patients’ choice. The risk of thrombosis in the AS patients with negative thrombophilia screening is small, therefore the prescription of combined oral contraceptive (COCP) is common practice. There is scarce information in the literature about the use of combined (estrogen-E2 and progestin) or progestin-only contraception on the disease outcome.

We present a case of cervical vasculitis on the background of AS disease on a patient with currently taking progestin-only contraception. We also review the literature for any evidence on the effect of the exogenous hormones on these conditions.

Case Report

A 27 year old nulliparous woman was seen as an emergency in gynaecology ward for complaints of severe vaginal discharge from a week. An initial assessment revealed a highly necrotic inflamed cervix hence an urgent referral was made to the colposcopy clinic. She was known to have low grade cervical intraepithelial...
neoplasia that was kept under surveillance. Due to the previous history and the suspicion of carcinoma of cervix the patient had a large loop excision of the transformation zone of the cervix. The histology was reported as acute inflammation of cervix with fibrinoid necrosis of vessel walls suggestive of vasculitis of the cervix (Figure 1). No cervical dysplasia was present. Her history of AS for the past 8 years prompted us to send an urgent referral to rheumatology. She was already under the care of the rheumatology clinic for the same and was managed on anti-inflammatory drugs (NSAID). A series of blood tests were performed including erythrocyte sedimentation rate, liver and renal function tests, C reactive protein, anti neutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), antiphospholipid, lupus anticoagulant, HLAB27 antigen and CRP to rule out systemic vasculitis. The HLA B27 was the only positive marker. The swabs for sexually transmitted infections were negative, CMV, hepatitis B surface antigen and HIV serology was normal. There was no other symptom or sign suggestive of localised or generalised infection. The infection was very meticulously investigated given the known possible association of vasculitis with a bacterial or viral infection. Hence, systemic vasculitis was ruled out.

For contraception she was taking COCP from the age of 18, being considered low risk for thrombosis with negative antiphospholipid and thrombophilia markers. However, lately she started experiencing rarely non-complicated migraines and was offered 3 monthly injectable MPA (150mg/ml). This was initiated four to five weeks prior to the onset of the cervical vasculitis. The patient reported also an increased need of NSAID for control of the back pain since this change in contraception medication. After the diagnosis of vasculitis she was advised not to renew the MPA injection and the contraception was reverted back to low dose Estradiol COCP.

At Colposcopy clinic follow up, the smear and colposcopic findings at the 6 months and then one year were normal. The 6 months Rheumatology follow up demonstrated improved pain and reduced NSAID need after the MPA injection was stopped and the COCP restarted. The patient stopped having migraines after the MPA was initiated and they didn’t occur again after the COCP was restarted.

Discussion

Two main questions have risen from his case: 1. The role of pre-existing AS in the development of cervical vasculitis and, 2. To what extent the change in the exogenous hormones from COCP to progestin-only had a role in the onset of vasculitis and the exacerbation of AS symptoms (backache, stiffness).

The isolated vasculitis is been rarely reported in the literature as presenting on the background of another autoimmune disease, but this association remains possible given the common pathogenesis mechanisms. Our patient had a history of AS which is a chronic inflammatory disorder with an autoimmune cause. It is known to be associated with prostatitis in men but its association with vasculitis of the cervix in women is rare. Hence, it was of primary importance to rule out a flare up and any systemic pathology due to vasculitis.

Since focal vasculitis may be the earliest indicator of a systemic disorder, the patients may be referred to the rheumatologists for a comprehensive evaluation.

Francke et al. [4] on a review of 11 cases of genital tract vasculitis, reported some cases of cervical vasculitis associated with systemic vasculitis like Wegeners granulomatosis, polymyalgia rheumatic, polyarteritis nodosa. Therefore the systemic vasculitis is usually ruled out usually by detailed history, clinical examination and laboratory studies [5,6]. This review showed that all patients with localised cervical vasculitis were managed expectantly without additional treatment to the excision [6-8].

Clinically, infections and vasculitis can present with similar clinical picture therefore excluding infection is essential in the diagnosis and correct management [9]. It could also manifest as a sequel to a variety of causes including cytomegalovirus infection and Chlamydia. Woywodt recommended a close analysis of the infection status in cases with localised cervical vasculitis. The uterine cervix is a site with a high encounter of microbial and viral antigens. A detailed microbiology assessment could be undertaken, with molecular approaches to demonstrate pathogens or antigens not routinely examined, that can have a role in the onset of this condition. Microbial phenotypic characteristics, biotyping and susceptibility testing are used for identification and differentiation [8]. PCR-based systems used to detect etiological agents of disease directly from specimen without the need of culture can been introduced in the clinical practice for the rapid detection of microorganisms. An amplified microbial DNA allows identification and better characterization of the pathogens [9].

In relation to the role of sexual hormones in the onset of vasculitis, there is evidence that they are considered to play a role in the immune answer, but further studies are needed to assess this role [10-12]. E2 and prolactin are considered to have pro-inflammatory effect whereas androgens and progesterone (Pg) have an anti-inflammatory effect [13]. The action is linked to
the activity of aromatase on the peripheral tissues. Inflammatory cytokines produced by macrophages alter the activity of aromatase that converts the androgens into E2. Subsequently E2 acts on the macrophages and increase the expression of cytokines closing this way a self-stimulation cycle [10,11,13,14]. Arteni et al. [15], have demonstrated that the direct action mechanism is dependent on the concentration of the hormones and the target tissue. This way, the high concentrations of E2 have anti-inflammatory effects, whereas the low E2 levels have pro-inflammatory effects.

AS being one of the very few autoimmune diseases with higher incidence in men, the testosterone (T) was considered to play possibly a role in the disease pathogenesis. There is a slightly higher level of T in males with AS compared to controls but still within normal range. However, evidence shows that there is no difference in the levels of T in women with AS compared to controls [16]. There is limited evidence on the androgenic effect of progestins on the symptom progression and pathogenesis of autoimmune disease. There is recognised risk in administering progestins only to patients that are on corticosteroids treatment for the risk of increased bone loss [17].

Regarding the use of exogenous hormones in the form of contraception or hormone replacement therapy (HRT) in autoimmune disease, the consensus is that these should be avoided in patients with positive antiphospholipid antibodies and risk of thrombotic or cardiovascular disease [18,19]. No specific information is available for the patients with systemic vasculitis but the recommendation is that estrogens are avoided in these patients because of the potential risk of ischemia. However, diseases as AS, dermatomyositis, non-generalised vasculitis are seen to be safe for prescription of exogenous hormones in stable disease and when accurate thrombophilia screening was carried out [15]. The patient discussed in this study, had normal investigations hence the initial decision to offer COCP for contraception.

In Jimenez-Balderas et al. study [20] administrating combined exogenous contraception to premenopausal and HRT to postmenopausal women with AS improved the peripheral arthritis significantly, and the functional class improved in most of the treated patients [21]. In a more recent study Mahendira et al. [22] evaluated the effect of COCP on the clinical outcomes in women with AS [21]. Out of the 571 women with AS recruited to participate in this study from the Spondilitis Association of America, 448 were users and 123 were non-users of COCP. The use of exogenous E2 was not associated with measurable effect on the onset, severity and biomarker levels.

In one reported case, the administered progesterone on a patient undergoing IVF was linked to the occurrence of panniculitis. Two days after the discontinuation of treatment the condition subsided [22]. The ethological factors for this condition are streptococcal infection, autoimmune disease and in 10% of cases drugs as oral contraceptives. Although the lesions, in this case, were not accompanied by vasculitis the subcutaneous inflammatory infiltrate developed through a similar pathogenic mechanism [23].

Huges [24] reviewed the existing literature on the impact Pg and synthetic progestins have on autoimmune disease [24]. The immune-mediated injury varied in different ways dependent on the concentration of hormones, engagement of different Pg receptors in different immune organs, immune cells and tissues targeted by an immune attack. The author underlined the evidence indicating that Pg modulates immune functions in vivo: post-pubertal predominance of autoimmune disease, systemic immunomodulation at times of high circulation of progesterone as pregnancy and luteal phase of the cycle, immunomodulation after Pg treatment.

**Conclusions**

The two conditions: localised vasculitis on a background of AS, could be linked to the fact that both have autoimmune pathogenesis, although the vast majority of the published cases of localised vasculitis appear without previous pathological background. Information specifically on the role of progestins only on these conditions is scarce, however, this patient had an exacerbation of symptoms and localised vasculitis acute onset after administration of medroxy progesterone therefore the injectable progestin was considered a trigger factor. This is supported by the fact that symptoms improved after the medication was interrupted. It can’t be concluded that progestin only contraception should be avoided in AS patients, but it can be raised awareness that the symptoms can exacerbate.

Further studies need to assess the biological effect of Pg and basic research is needed to clarify the cellular mechanisms by which E2 and Pg modulate the immune response and immune disease separately and together.

These isolated cases need to be reported to constitute a base for collective evidence later on.
References


