Desquamative Inflammatory Vaginitis as an extra-articular Manifestation of Rheumatoid Arthritis?

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Abstract
We report four women with seropositive Rheumatoid Arthritis (RA) presenting with concomitant Desquamative Inflammatory Vaginitis (DIV). No convincing evidence emerged establishing a causal connection between RA and DIV, or indicating that DIV was an extra-articular manifestation of RA. Similarly, use of rituximab was not shown to be a causal factor in pathogenesis of vaginitis.

INTRODUCTION
Rheumatoid arthritis (RA) affects 1-2% of the population worldwide. It is the most common inflammatory joint disease, affecting women two to three times more commonly than men [1]. It is a complex disease with a combination of risk alleles from different susceptibility genes predisposing to development of the disease, following exposure to unknown environmental factors [2].

Extra-articular manifestations of RA not directly related to the locomotor system are by no means uncommon [1-5]. Several studies have shown that presence of extra-articular manifestations varies directly with the severity and manifestations of rheumatoid disease [6,7]. Extra-articular manifestations in RA include vasculitis, neuropathy, pericarditis, pleuritis, Felty’s syndrome, ophthalmologic manifestations (e.g. keratoconjunctivitis sicca, scleritis, episcleritis and peripheral ulcerative keratitis), glomerulonephritis, rheumatoid lung disease, amyloidosis, and rheumatoid nodules [1-8]. However, there are no studies about the vaginal manifestations of rheumatoid arthritis.

Desquamative inflammatory vaginitis (DIV) is an uncommon and severe form of chronic vaginitis causing purulent discharge, vestibulo-vaginal irritation, and dyspareunia [9,10,11]. It predominantly occurs in Caucasians and although diagnosed in a wide age range, its occurrence peaks in perimenopausal women [12,13]. DIV syndrome has unknown etiology and is frequently undiagnosed. It is characterized by vaginal inflammation with a vaginal rash and purulent discharge with microscopy revealing a marked increase in inflammatory cells, predominantly polymorphonuclear leukocytes and parabasal epithelial cells, together with abnormal vaginal flora or dysbiosis [9,10,14,15]. The term desquamative inflammatory vaginitis first was introduced by Gray and Barnes in 1965 when they described six women with a “reddened” vagina and “numerous pus cells with oval and round parabasal cell” [14]. Gardner published the first case series three years later with eight patients who had similar clinical presentation and no response to antimicrobial treatment [9]. It was only after three decades that Sobel described desquamative inflammatory vaginitis in 51 women and successful treatment with 10% hydrocortisone and 2% clindamycin [10]. DIV is now considered as, by no means uncommon and thought to represent an autoinflammatory or autoimmune disease precipitated by estrogen deficiency.

There have been no studies documenting the association of RA with DIV. We report four women with diagnosed RA seen at a university- based vaginitis clinic presenting with vaginal symptoms and manifestations of DIV.

CASE REPORTS
Case 1
A 46-year-old female with longstanding RA well controlled on rituximab, presented to the clinic in December 2014 with purulent vaginal discharge. She was diagnosed with pyoderma gangrenosum and desquamative inflammatory vaginitis and was prescribed 10% hydrocortisone 5 g intravaginal once daily. Her DIV, purulent vaginitis was thought to be due to rituximab and the possibility was discussed with her Rheumatologist. Her symptoms responded to vaginal hydrocortisone for 3 months, but she had a relapse of DIV and clobetasol ointment BID was added to the regimen. At this point, she was still on rituximab for RA. 3 Months later, hydrocortisone and clobetasol doses were reduced due to weight gain and facial puffiness and well controlled vaginal symptoms. However, her DIV relapsed while on reduced doses of 10% hydrocortisone and clobetasol. She had also switched from rituximab to tocilizumab. In the following 5 months on increased topical steroid therapy, she reported continuous improvement.
in DIV leading to full remission, allowing vaginal corticosteroid medications to be gradually discontinued.

**Comment:** This patient suffered from severe longstanding but well-controlled rheumatoid arthritis benefitting from rituximab. She made a successful transition from rituximab to tocilizumab and after prolonged local vaginal steroid therapy achieved full resolution of her DIV. The role of rituximab in causation of DIV was never established.

**Case 2**

A 60-year-old female with past medical history of rheumatoid arthritis well controlled on rituximab infusions, methotrexate and folic acid was referred for chronic vaginal discharge and pain. She presented to the clinic in December 2011 with abnormal discharge. Examination findings showed vestibular erythema and erosion and diffuse vaginal rash. DIV was suspected on the basis of microscopic findings and patient was started on 10% hydrocortisone vaginal cream once daily and topical estradiol twice weekly. Her past medical history also included Hashimoto thyroiditis and Sjogren’s syndrome. On 1 month follow up, her vaginal symptoms were considerably improved with accompanying improvement in examination findings. Vaginal hydrocortisone was reduced to 5 x week and topical vestibular steroids was started. For the next 11 months, DIV remained in controlled remission and the same regimen was continued, however acute vulvovaginal candidiasis developed, treated with induction and maintenance therapy with oral fluconazole. Months later, she had a mild DIV relapse presenting with burning and irritation. Globetosol ointment was added to her regimen. However, her DIV remained uncontrolled with florid vestibulitis in the following 3 months and discontinuation of rituximab was recommended. Even after trying tacrolimus and intramuscular Kenalog for 12 months later her DIV remained uncontrolled. She was started on intravaginal sulfanilamide and niacinamide 4 g once daily x 6 months and DIV showed moderate improvement only. At the time, she was treated with methotrexate and hydroxychloroquine for RA. Subsequently she restarted rituximab for RA flare up. She discontinued her medications for DIV, with her only symptom being residual dyspareunia. Currently, RA is moderately well controlled while still receiving rituximab. Full remission of DIV was never achieved in spite of all local modalities of therapy.

**Comment:** Longstanding RA, never completely controlled on hydroxychloroquine, methotrexate and rituximab, simultaneously developing florid, severe DIV. Later demonstrating incomplete DIV resolution in spite of topical and systemic steroid therapy and discontinuation of rituximab. Once more, causal relationship between RA, rituximab and DIV was never established.

**Case 3**

A 50-year-old female with past medical history of RA, well controlled on rituximab infusion (1 x year) was referred in October 2017 for uncontrolled DIV present for 18 months, she had been treated with clindamycin, boric acid and 10% hydrocortisone in the past. At the time of presentation, her dominant symptoms were copious discharge, burning, pain and itching. Examination findings showed vestibular inflammation and diffuse rash in the upper third of vagina. Saline microscopy showed 4+ increase in white cells, 3+ parabasal cells, absence of normal flora and a pH of 5.5. DIV secondary to rituximab was suspected and she was advised to start intravaginal clindamycin 2% and HC once a day. She was also advised to consider discontinuing rituximab. At 1 month follow up, she was asymptomatic with improved vaginal physical examination and microscopic findings. DIV was in controlled remission and she was advised to decrease clindamycin and hydrocortisone dosage. Two months later, however she presented with DIV relapse after discontinuing local anti-inflammatory therapy. She restarted 10% hydrocortisone 4 g per vagina and two months later, her symptoms had dramatically improved, examination as well as pH and microscopy findings were normal and DIV was in controlled remission. She was advised to discontinue vaginal hydrocortisone and her DIV has entirely resolved and RA is well controlled on rituximab.

**Comment:** This patient presented with DIV of 18 months duration and RA well controlled on rituximab infusion. Although a causal relationship between DIV and RA was suspected, the role of rituximab in causation of DIV is unlikely.

**Case 4**

A 56-year-old female presented to the clinic in November 2013 complaining of burning on micturition, copious vaginal discharge, itching and dyspareunia. Examination findings showed erythematous vagina, edematous vulva with bilateral fissures while saline microscopy showed 2+ increase in white cells, 3+ parabasal cells, absence of normal flora and a pH of 5, compatible with diagnosis of DIV. She was started on intravaginal 2% clindamycin. At her 2 months follow up, she was asymptomatic, DIV had dramatically improved with residual focal vestibulitis and the same regimen was continued at lower dose and estradiol per vagina twice weekly was added. One month later, clindamycin was decreased to three times weekly and estradiol per vagina added. She remained asymptomatic with well controlled DIV over the next 1 year. During this period, she was diagnosed with seropositive Rheumatoid arthritis and was started on etanercept (TNF inhibitor) which was followed by DIV relapse while on low dose 2% clindamycin maintenance. Clindamycin dose was increased to once weekly and her examination findings responded. Over the next 5 years, her DIV remained controlled, asymptomatic but smoldering with declining dose of maintenance clindamycin.

RA was well controlled on tofacitinib. Her last visit was in February 2020 and although entirely asymptomatic, low grade smoldering DIV was present based upon pH and saline microscopy and the same regimen was continued. Currently she is asymptomatic in terms of DIV, on vaginal clindamycin 2% cream twice monthly.

**Comment:** Her initial presentation of DIV preceded onset of RA and therapy thereof. Severe DIV responded well to vaginal anti-inflammatory therapy with 2% clindamycin but has never completely resolved although now asymptomatic. Her RA responded well to tofacitinib. Relationship between DIV and RA possible but unproven.

**DISCUSSION**

Despite the fact that extra-articular manifestations have been studied in numerous RA cohorts, there is no uniformity in their...
definition or classification. Extra articular manifestations occur in 17.8–40.9% of RA patients and 1.5%–21.5% of them present in the most severely affected [16, 17].

The prevalence of extra—articular manifestations of RA has declined in recent years, with the timing and pattern of the decline indicating that disease-modifying RA treatments may be changing the natural history of the disease [18–20]. Trends for specific extra-articular manifestations varied, showing linear declines in fibromyalgia syndrome, increases in RA lung disease, possibly reflecting increased diagnostic sensitivity with early recognition and treatment being the key to decrease mortality [19, 21]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) are primarily used for treatment of RA. This was followed by methotrexate and a major advance followed the advent of infliximab, which targets tumor necrosis factor α (TNFα). Thereafter numerous biological drugs inhibiting interleukin-6 (IL-6) and cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), and Janus kinase (JAK) inhibitors, were approved in succession. These drugs being highly effective against RA, made it possible to raise the treatment goals for RA [22].

In order to establish whether DIV represents an extra-articular complication of RA, a number of criteria need to be satisfied. High prevalence of DIV in RA greater than what one may anticipate. In the last two decades, more than 200 patients with DIV have been seen at the Vaginitis clinic [11]. Accordingly, 4 patients in the last 9 years failed to meet the criteria of increased occurrence suggesting a causal link. In a review of 200 patients in our clinic as reported by Reichman and Sobel, a search for associated clinical diagnostic entities was undertaken and no association between DIV and other autoimmune and autoinflammatory conditions emerged [10–12]. Another factor suggesting an association could be a temporal relationship particularly in relation to activity and control of RA, correlating with occurrence, expression or activity of DIV. On the basis of the four cases reported here, no clear association was evident. DIV could present, exacerbate or relapse without any change in RA activity. Likewise, no improvement in DIV necessarily followed improved management of RA.

Complicating any association between RA and DIV is the role of rituximab and other biologics now in use for the treatment of RA. No other biologics have been associated with vulvovaginal disease; however, several case series and case reports have implicated rituximab in causation of vulvovaginitis including pyoderma [23, 24]. Although, three of the four RA patients reported in the current series received rituximab prior to onset of DIV, a clear causal relationship could not be established, in that DIV never resolved or improved with discontinuation of rituximab alone. Stopping rituximab in women with active symptomatic DIV simultaneously intensively treated with DIV specific anti-inflammatory agents precludes establishing a causal role.

CONCLUSION

Although both rheumatoid arthritis and DIV are considered non-infectious, auto-inflammatory diseases, no causal relationship could be established. In patients with RA well controlled on rituximab in whom DIV is newly diagnosed, there appears no convincing evidence that rituximab should be discontinued and an alternative biologic initiated. Such action may be considered only when DIV is refractory to appropriate vaginal anti-inflammatory treatment.

REFERENCES