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REACTIVE ARTHRITIS – TWO DIFFERENT CASE REPORTS

Abstract

Reactive arthritis (ReA) is classified as an autoimmune condition that includes a classic triad of symptoms, conjunctivitis, urethritis and aseptic peripheral arthritis (Reiter's syndrome), occurring in young males within one month of a primary urogenital or gastrointestinal infection. Hereby, we describe from the dermatological point of view two cases: the first one, a patient with a seronegative polyarthritis receiving specific immunosuppressive treatment with leflunomide and sulfasalazine, which evolved to a spondyloarthritis; the second one, a classic reactive arthritis diagnosed based on the oculo-urethro-synovial triangle.

Key words:

reactive arthritis, reiter syndrome, circinate balanitis

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INTRODUCTION

Reactive arthritis (ReA) is classified as an autoimmune condition that include a classic triad of symptoms – conjunctivitis, urethritis and aseptic peripheral arthritis (classic ReA or Reiter's syndrome) – typically occurring in young males within one month of a primary urogenital or gastrointestinal infection [1, 2]. Recognized in the literature as the "can't see, can't pee, and can't climb a tree" syndrome, also referred as Fiessenger-Leroy-Reiter, Reiter's syndrome was firstly described during the World War I by the German physician Hans Reiter, emphasizing the inflammatory connection between the eye, the urinary tract and synovium in a genetic susceptible host [1, 2, 3].

Among rheumatologists, ReA is classified as a seronegative spondyloarthropathy (along with ankylosing spondylitis, psoriatic arthritis, juvenile spondyloarthritis and arthritis associated

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with inflammatory bowel disease), a heterogeneous group of chronic inter-related inflammatory arthropathies affecting synovium, entheses and specific extra-articular sites [2].

While the clinical pattern of ReA is commonly based on HLA-B27-linked oligoarthritis (large joints of the lower limb and/or sacroiliac joints), a significant number of patients with ReA develop characteristic extra-articular features including mucocutaneous lesions, namely keratoderma blennorrhagicum, circinate balanitis, ulcerative vulvitis, urethritis, and ocular inflammation (conjunctivitis, acute iritis) as well [2, 4]. Table 1 summarizes the clinical manifestations of ReA, while table 2 is intended to help dermatologist to distinguish between different entities belonging to the spondyloarthritis group as well as rheumatoid arthritis [2, 5]. Although in certain cases ReA may be a self-limiting condition, a chronic progressive, highly disabling pattern of the disease is also recognized, requiring aggressive treatment not only directed to the underlying infection but also including immunosuppressive medication, even TNF-blocking agents in refractory ReA [2, 5].

In this article we describe, from the dermatological point of view, two cases: the first one, a patient with a long history of seronegative polyarthritis treated with immunosuppressive drugs (leflunomide and sulfasalazine) which was finally classified as having a spondylarthritis; and the second one, a patient with a typical diagnose of

Table 1. Clinical manifestations of Reactive arthritis [1]

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|--|
| ■ Urogenital: urethritis, cervicitis, prostatitis |
| ■ Rheumatologic: arthritis, enthesitis |
| ■ Ophthalmologic: conjunctivitis, uveitis, keratitis |
| ■ Dermatologic: keratoderma blennorrhagicum, circinate balanitis/vulvitis, nail dystrophy |
| ■ Oral: erythematous macules, papules, plaques, erosions |
| ■ Visceral: cardiac, renal or neurologic manifestations |

classic reactive arthritis based on the oculo-urethro-synovial triangle.

CASE 1

A 32 year-old male patient with a 10-years history of seronegative polyarthritis treated with a combination of leflunomide and sulfasalazine was admitted for high fever, malaise, painful and swollen peripheral joints (distal interphalangeal joints, knee, ankle), inflammatory low back pain, dactylitis as well as cutaneous manifestations characteristic for balanitis circinata (fig.1); no ocular or gastro-intestinal symptoms were identified; no previous urogenital infection or enteritis was reported.

The laboratory studies revealed anemia (hemoglobin 10.6g/dl), leukocytosis (leukocytes 12500/mm³) with neutrophilia (neutrophils 70%) and lymphopenia (lymphocytes 10%), highly elevated ESR (80 mm/h) and C-reactive protein (150 mg/l), negative rheumatoid factor, and negative antinuclear antibodies. HLA-B27 antigen positivity was detected.

The urethral smear was negative for *Chlamydia trachomatis* (PCR), *Neisseria gonorrhoea* (PCR, culture), *Mycoplasma spp.* but positive for *Candida spp.* (culture); in addition, the microbiological exam of samples from urethra were positive for *E.coli*. Stool was negative for *Salmonella spp.*, *Shigella spp.* and *Yersinia spp.* (culture). Serological tests for *Chlamydia trachomatis* (IgA/IgM/IgG EIA), *Chlamydia* and *Mycoplasma pneumoniae* (EIA), syphilis (VDRL, TPHA), HIV, hepatitis B and C viruses were also negative.

Based on clinical, biological and imaging studies (spine and sacroiliac joints X-rays, sacroiliac joints computer tomography, musculoskeletal ultrasound) the diagnosis of spondyloarthritis was established.

Oral antibiotics (ciprofloxacin 500mg twice daily for 14 days, followed by doxycycline for another two weeks) along with non-steroidal anti-inflammatory drugs (NSAIDs) were started, while Disease Modifying Anti-Rheumatic Drugs (DMARDs) were maintained at the previously recommended doses (20 mg leflunomide, 3000 mg sulfasalazine).

Only minor improvement of the musculoskeletal symptoms and lab abnormalities (chronic inflammation, anemia) were reported; moreover, one month later the patient returned in the dermatology outpatient department with a new dermatological picture (fig. 2).



Fig. 1. Balanitis circinata.



Fig. 2. Hyperkeratotic plaques on glans penis (a few months later).



Fig. 3. Localized psoriasis (two years later).

The treatment was further reconsidered: we discontinued leflunomide, methotrexate 20mg once weekly, was added to sulfasalazine which was progressively increased to 3000 mg daily; we restarted doxycycline 200 mg/day and topical steroids (Mometason cream once daily) on the genital area.

Two years later, the patient was reported for a routine dermatological assessment; he was under biological therapy (Infliximab) with significant improvement of his polyarthritis but presenting cutaneous lesions of psoriasis (fig. 3).

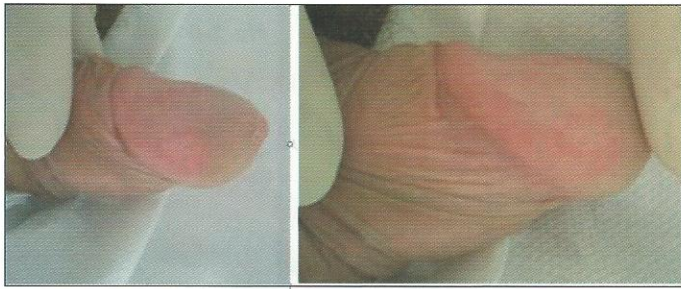


Fig. 4. A. Circinate balanitis, B. Close view.

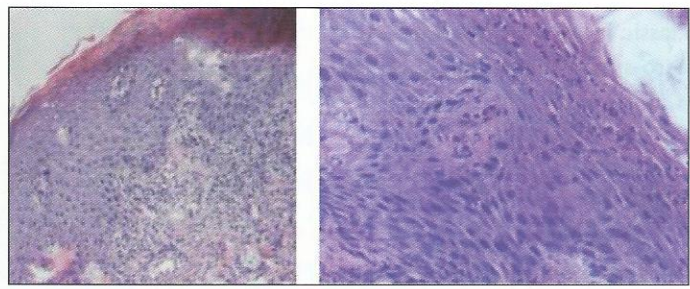


Fig. 5. Radiological examination: signs of sacroiliitis. The presence of syndesmophytes on the lumbar spine.

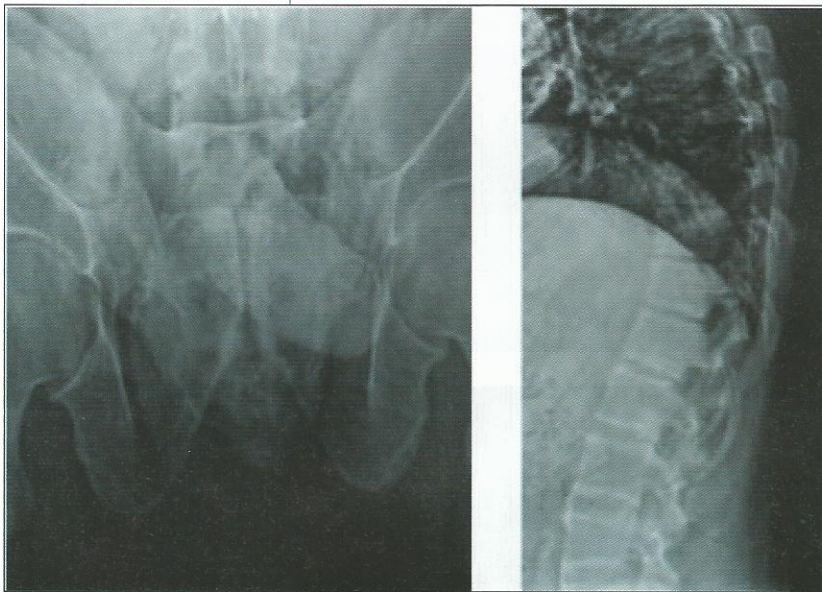


Fig. 6. A. HEX100: Hyperkeratosis and acanthosis. B. HEX200: intracorneal pustule.

CASE 2

We present the case of a 26-year old male reported from primary care in the outpatient dermatology department for a medical appointment. The patient had a two-year history of periodic episodes of vesicles and small papules typically occurring on the glans penis without any apparent trigger factor, and chronic inflammatory low back pain.

Clinical exam revealed vesicles and small papules mainly located on the glans penis, together with coalesced superficial erosions with a sharply demarcated pattern subsequent to the rupture of these lesions, very suggestive of circinate balanitis (fig. 4). We conducted a punch biopsy with histopathologic examination which demonstrated hyperkeratosis, acanthosis and evidence of intracorneal pustule (fig. 5).

In addition, the routine rheumatologic assessment identified left ankle arthritis and evidence of axial involvement (spine and sacroiliac joints), while the radiologic evaluation showed characteristic signs of asymmetrical stage II sacroiliitis and syndesmophytes particularly located in the lumbar spine (fig. 6). Concomitant acute bilateral conjunctivitis was also confirmed.

Based on clinical, histological and imagistic findings, with a background of high acute phase reactants (erythrocyte sedimentation rate, C-reactive protein level up to 2.5 the normal upper limit) and HLA-B27 positivity the diagnosis of ReA (Reiter's syndrome) was proposed. Oral NSAIDs (diclofenac 150 mg daily) and sulfasalazine (3 grams daily) were started and subcutaneously etanercept (50 mg weekly) was further added after six months as no significant improvement of both dermatologic and

Table II. Comparison between psoriasis, reactive arthritis and rheumatoid arthritis

	Psoriatic arthritis	Classic reactive arthritis (Reiter's syndrome)	Rheumatoid arthritis
Arthritis	Five patterns: axial; small joints of the hands and feet; peripheral oligoarthritis; isolated distal interphalangeal joint involvement; arthritis mutilans	Peripheral oligoarthritis mainly in the lower limb; axial involvement (including sacroiliitis), enthesitis	Small joints
Extraarticular features			
Cervicitis, urethritis, mucos membrane lesions	Absent	Present	Absent
Uveitis, conjunctivitis	Possible	Present	Absent
Psoriasis	Present	Negative	Negative
HLA B27	Negative	Positive	Negative
Rheumatoid Factor	Usually negative	Negative	Positive
Anti-CCP antibody (anti-citrullinated protein antibodies)	Negative	Negative	Positive

rheumatologic involvement was reported. After three months of biological therapy, no dermatological or musculoskeletal complains were detected.

DISCUSSION

The concept of spondyloarthritis was recently addressed as new insights in the pathological pathways, diagnostic tools as well as diagnostic and classification criteria were described [2, 5]. Moreover, the wide spectrum of clinical features reported in distinct disorders belonging to this group, comprising at least four patterns such as axial disease, peripheral arthritis, enthesitis and extra-articular features allows the diagnosis based on clinical grounds [2, 5].

The first case reported in this paper was primarily classified as seronegative polyarthritis and treated with a combination of synthetic DMARDs; however, an overlap of symptoms developed during the course of the disease meaning both axial symptoms (inflammatory low back pain) and peripheral arthritis including distal small joints, as well as dactylitis, circinate balanitis, and, psoriatic skin lesions in a genetic predisposed host (HLA-B27 positivity) guiding towards a challenging diagnosis. Moreover, the pattern of articular involvement suggested a psoriatic arthritis without skin symptoms (psoriatic arthritis sine psoriasis), while the typical skin manifestations appeared only after many years.

As already described in literature, ReA can coexist with psoriasis [2, 5, 6, 7, 8]; authors from Serbia presented a rare but concomitant

appearance of ReA and psoriasis vulgaris in the same patient [6]. Reactive arthritis was diagnosed according to the specific clinical feature, while HLA typing demonstrated a positive HLA-B 27 antigen.

The second case typically describes the classic triad of ReA comprising ocular (acute bilateral conjunctivitis), genital (circinate balanitis) and musculoskeletal (peripheral asymmetric pauciartthritis and sacroiliitis) signs. Although the diagnosis was rapidly confirmed and specific NSAID and DMARD therapy started, both skin lesions, low back pain and ankle arthritis were persistent and relatively unchanged, requiring biological therapy. The lack of response to medication is not uncommon in certain patients with ReA; patients with persistent and refractory arthritis to conventional treatment could be considered as good candidates for anti-TNF agents; although small open-label studies have confirmed the efficacy of TNF inhibitors for the above mentioned patterns of ReA, no controlled data are yet available [5].

In conclusion, the diagnosis of ReA could be challenging in certain patient population, particularly in cases where the articular pattern is atypical, or the triggering not detected infection. Besides, the dermatological manifestations usually help to improve the diagnosis of different spondyloarthropathies.

Due to the overlapping symptoms in immune-mediated disorders, the tight teamwork between dermatologists and rheumatologists remains really important in clinical practice, emphasizing their role in early diagnosis, comprehensive monitoring and multidisciplinary management as well as improved patient education.

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