

Bacterial invasion as a key factor in progression of reactive arthritis on example of clinical case

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Introduction

- **Reactive arthritis is a condition associated with bacterial infections of the urogenital and gastrointestinal tract, which trigger the onset of the disease, and also play a role in the progression of inflammatory-destructive processes in the musculoskeletal system.**
- **This clinical case illustrates the effect of repeated bacterial invasions on the development of chronic reactive arthritis with persistent course of the disease.**

Reactive arthritis

- Reactive arthritis (ReA) is sterile inflammation of the synovial membrane, tendons and fascia triggered by an infection on a distant site, usually gastrointestinal (GI) or urogenital.
- It is frequently associated with the human leukocyte antigen (HLA)–B27 haplotype and is classified in the category of seronegative spondyloarthropathies.
- ReA predominantly affects young adults in the 20–40 age group, and affects men more than women (ratio 3:1).
- Adolescents and young men are most likely to develop ReA after a genitourinary infection, whereas young children tend to have the postdysenteric form.

Etiology and pathophysiology

- ReA has been associated with gastrointestinal (GI) infections often caused by Shigella, Salmonella, Campylobacter, as well as with genitourinary (GU) infections (Chlamydia Trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum).
- The mechanism by which the interaction of the inciting organism with the host leads to the development of ReA is not known. But there are several pathogenetic theories.

Pathogenetic theories include:

- Molecular mimicry theory (similarity exists at the molecular level between the HLA-B27 molecule and the inciting organisms, allowing the triggering of an immune response);
- Role of HLA-B27 as a receptor for certain bacteria;
- Defective class I antigen-mediated cellular response (HLA-B27 molecule may be a defective molecule associated with an aberrant cytotoxic T-cell response).

Clinical presentation of ReA

The onset is usually acute and characterized by malaise, fatigue, and fever. It usually develops 2-4 weeks after a genitourinary (GU) or gastrointestinal (GI) infection.

Classic triad for ReA:

- Arthritis - asymmetrical, predominantly lower-extremity with redness, swelling, pain and warmth in and around the affected joint; may be associated with heel pain, lower back pain, sometimes with early myalgias;
- Urethritis - initial nongonococcal urethritis, with frequency, dysuria, urgency, and urethral discharge;
- Conjunctivitis - in addition to conjunctivitis, ophthalmologic symptoms that include erythema, burning, tearing, photophobia, pain, and decreased vision;



https://en.wikipedia.org/wiki/Reactive_arthritis#/media/File:SOA-arthritis.jpg



<http://www.pcds.org.uk/clinical-guidance/reiters-syndrome#!prettyPhoto>

Clinical classification of ReA

Course of the disease	Acute, subacute, chronic relapsing
Activity of the disease	0 (absent), I (low), II (moderate), III (severe)
Clinical and morphologic characteristics	
Joints	Asymmetrical lesions presenting as olygoarthritis, monoarthritis or polyarthritis
Urogenital system	Urethritis, prostatitis, cystitis, balanitis (balanitis circinata), endocervicitis, adnexitis, pyelonephritis
Eyes	Reactive iritis, uveitis, conjunctivitis, episcleritis
Muscles and tendons	Enthesopathy, tendinitis, tendovaginitis, myalgia, heel pain, heel spurs, bursitis
Skin and mucosae	Keratoderma blennorrhagicum, hyperkeratosis, onychodystrophy, psoriasis-like skin lesions, erosions of lips, tongue, cheeks mucosae
Cardio-vascular system	Myocarditis, endocarditis, rare – aortic insufficiency

Due to Ukrainian association of rheumatologists, 2004

Diagnostics of ReA

- Recognition of the typical clinical features of spondyloarthritis;
- Evidence of urogenital infection (symptoms and signs of urethritis and microscopic confirmation by a Gram-stained urethral smear; mucopurulent cervicitis in women) or gastrointestinal infections (stool culture);

Essential investigations:

- Full screening for sexually transmitted infections (STIs), including HIV; gastrointestinal infections.
- Acute phase response: erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP);
- Full blood count (FBC).
- Urinalysis (to check for renal pathology).
- Synovial fluid analysis (where septic arthritis is suspected)

Often used investigations:

- HLA-B27.
- X-rays of affected joints, spine, sacroiliac joints, ultrasonography of affected joints, entheses.
- Electrocardiogram.
- Ophthalmic evaluation including slit lamp assessment.
- Liver and kidney function tests.

Treatment of ReA

- Rest with the restriction of physical activity, especially weight-bearing activity.
- **Non-steroidal anti-inflammatory drugs (NSAIDs):**

Nonselective: Diclofenac sodium 100-150 mg per day;

Selective: Meloxicam – 7,5-15mg per day; Celecoxib – 200 mg 1-2 times per day;

- **Antimicrobial therapy** for any genital infection identified for 2-3 months or more:

Macrolides: Azithromycin 0,5 g per day;

Tetracyclines: Doxycycline 0,1 g 3 times per day;

Fluoroquinolones: Ofloxacin 0,2 g 3 times per day; Ciprofloxacin 0,5 g 3 times per day, etc.

- **Corticosteroids** – intraarticular methylprednisolone 0,1-40mg/day depending on the size of the joint; systemic usage in severe case, ineffective previous therapy;
- **Sulphasalazine, Methotrexate** indicated where disabling symptoms persist for three or more months, or earlier in severe cases or where evidence of erosive joint damage is present.

Prognosis

- Reactive arthritis typically has a self-limited course, with resolution of symptoms by 3-12 (usually 4-6) months, even in patients who are acutely incapacitated.
- Postdysenteric cases are associated with a better prognosis than postvenereal cases. The presence of HLA-B27 and infections triggered by Yersinia, Salmonella, Shigella, Chlamydia may predict a more prolonged course and severe outcome. A fatal outcome is seldom reported.
- ReA has a high tendency to recur (15-50% of cases), particularly in HLA-B27–positive patients. A new infection or other stress factor could cause reactivation of the disease.
- About 15-30% of patients with ReA develop a long-term, sometimes destructive, arthritis or enthesitis or spondylitis.
- The presence of hip-joint involvement, an ESR higher than 30, and unresponsiveness to NSAIDs probably portend a severe outcome or chronicity in ReA.

Our patient

- Name: A.P.C.
- Sex: Male
- Age: 43 years
- Location: Kharkiv
- Occupation: Not working, disability 3d degree.

Complaints

- **Complaints of dull pain in the knee, ankle, hip joints, in the cervical, lumbosacral spine, morning stiffness of the joints for 2,5 to 3 hours. The pain is permanent, more pronounced in the right knee and right hip joints, worsens with movements, decreases with the intake of NSAIDs (diclofenac).**
- **Also patient complains on swelling and pain in his left wrist that worsens when he fists his hand.**

Anamnesis of present illness

- July 2010 – 2 weeks after **Salmonellosis** first acutely appeared **pain in the right knee, ankle joints, lower back pain, heel pain and burning, redness of both eyes**. Patient denied the presence of urethritis. He did not seek medical help, occasionally took NSAIDs.
- Nov 2010 - joint pain worsened, right hip become affected; after referral to a rheumatologist, he was admitted to Kharkiv hospital #28, where **high titers of mycoplasma and ureaplasma** were detected (ELISA and PCR). Was made diagnosis of: urogenital reactive arthritis and he was treated with doxycycline, NSAIDs, dexamethasone, state has improved but still there was moderate pain and slight limitation of joint mobility. In 2011 was made diagnosis of chronic reactive arthritis (inpatient treatment).
- Dec 2012 – tried to “increase the immunity” by eating raw eggs and was hospitalized with Ds: **Salmonellosis** (17.12-25.12); after had hospitalization with Ds: **Lyme's disease, chronic course** (26.12-15.01.13). After this patient's state worsened significantly - intensified pain in affected joints with enlargement, redness, restriction of movements; also become affected left wrist joint, temperature increased up to 37,4C. January 2013 – inpatient treatment in rheumatology department with diagnosis: Reactive arthritis, chronic course, activity of 2 grade, polyarthritis, right-sided sacroiliitis 3grade, functional impairment 2 degree. The patient was treated with methotrexate, sulphasalazine.
- Subsequently, the patient was annually hospitalized in a rheumatology department.

Anamnesis of life

- Patient is not working ,denies smoking, alcohol and drug abuse;
- Postponed diseases: URVI, tonsillectomy at the age of 9 years;
- Denies viral hepatitis, tuberculosis;
- Had no traumas, surgeries, allergic reactions;

Objective examination

- General state of the patient is of **moderate severity** due to his articular status, he's oriented to the time, place, himself; **uses a cane for walking; Tredelenburg gait.**
- Height 191 cm weight 90 kg , BMI= 24.7 kg/m²; t - 36,8 C.
- Skin is pale, clean; skin turgor, moistness is preserved; visible mucous membranes are clean, moist; subcutaneous adipose tissue is developed moderately, distributed symmetrically. Lymphatic nodes are not palpable. No edemas.
- Thyroid gland is not enlarged;
- Lungs: resonance percussion sound, vesicular breathing over both lungs fields, RR -17/';
- Heart borders are not enlarged, heart tones are clear, loud, rhythmic; BP dex - 129/85, BP sin - 130/83, radial pulse is synchronous, rhythmic at 88bpm.
- Abdomen: abdomen is painless on superficial and deep palpation in all regions. Liver at the costal margin, painless; spleen is not palpable. Pasternatskiy sign is negative on both sides. Urination is free, painless.
- Musculoskeletal system examination – on the next slide.

Musculo-skeletal system examination

- Left wrist is moderately swollen, slightly painful on palpation and when the patient fists his hand; there is no increased skin temperature or skin color changes.
- Vertebral column: **scoliotic posture**; spine mobility: Schober test -15 cm.
- Pelvis and hip joints: there is a **right lateral pelvic tilt**; **Tredelenburg gait** is present; **pelvis compression tests** are positive on the right side.
- Knee joints - smoothness of the contours, edema, crepitation during movement more pronounced in the right knee, increased skin temperature above the right knee joint.
- Ankle joints - smoothness of contours, puffiness, more pronounced on the right, tenderness in palpation with slight restriction of movements; there are signs of **Achilles tendinitis**.

Amplitude of movements in joints

Type of movement	Hip joints	Knee joints	Ankle joints
Flexion (flex)	Right: 120° , left: 110°	Right: 90° , left: 90°	Right: 120° , left: 120°
Extension (ext)	Right: 150° , left: 160°	Right: 160° , left: 170°	Right: 80° , left: 80°
Normal range (ext/flex)	180°/75°	180°/40°	70°/130°

Knee joints

- Smoothness of the contours of the knee joints, edema, crepitation during motion more pronounced in the right knee, increased skin temperature above the right knee joint.



Plan of survey

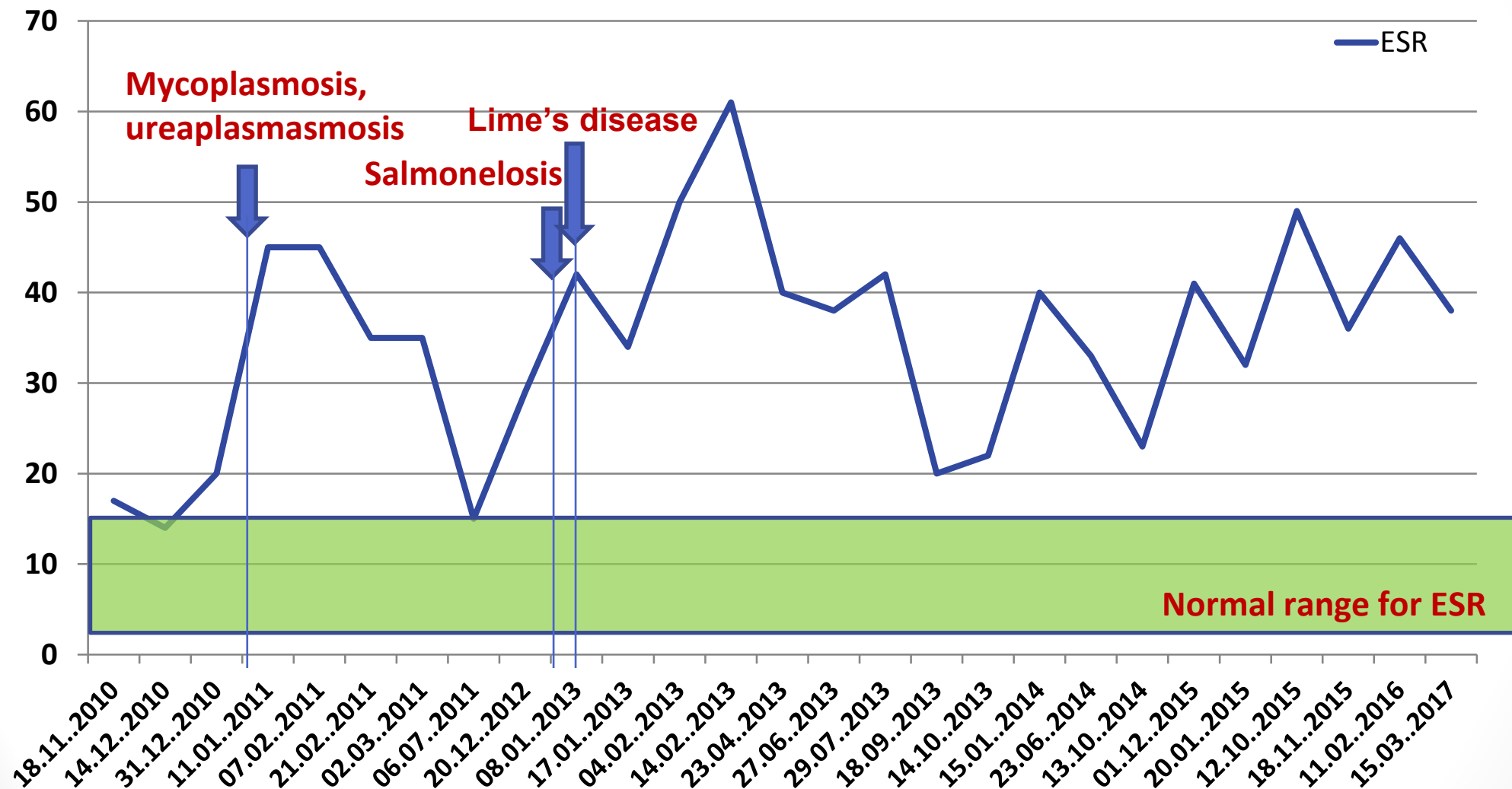
- Full blood count, urinalysis
- Blood analysis for urogenital infections, tests for HIV, syphilis
- Biochemical panel
- Serology including HLA-B27
- Chest X-ray, X-ray of knees, feet, hips, sacroiliac joints, spine
- ECG
- Consult of an orthopedist-surgeon

Full blood count

Options	Results	Normal range
Hemoglobin, g/L	138	130,0 – 160,0
Erythrocytes $\times 10^{12}/l$	4,6	3,7-4,7
Color index	0,9	0,85 – 1,15
Leukocytes $\times 10^9/L$	8,8	4,0 – 9,0
Erythrocyte sedimentation rate (ESR), mm/h	38	2-15
Stab neutrophils, %	4	1-6
Segmented neutrophils, %	60	47-72
Eosinophills, %	0	0,5-5,0
Basophils, %	0	1-1,0
Lymphocytes, %	27	19-37
Monocytes, %	6	3-11

Conclusion: increased ESR

Dynamic changes of ESR 2010-2017 yrs.



Urine analysis

Options	Results	Normal range
Specific gravity	1,021	1,001-1,040
pH	6,0	5,0-7,0
Protein, g / l	Not detected	to 0.033
Glucose	Not detected	absent
Leucocytes, cells/hpf	1-3	6-8
Epithelium, cells/hpf	0	≤15-20
Bacteria	Not detected	absent

Conclusion: all parameters within the normal range

Biochemical and serological panel

Options	Results	Normal range
C-reactive protein, mg/l	12	<5
Sialic acids, mmol/l	2,49	1,8-2,7
Seromucoid	5,9	1-5 S-H
Urea, mmol/l	4,8	1,7-8,3
Creatinine, mg/dl	0,088	0,7-1,4 (men)
ALT, U/l	0,21	<41 (men)
AST, U/l	0,17	<40 (men)
ANA (Anti-nuclear antibody)	1,0 positive	negative
HLA-B27	negative	negative

Conclusion: increased CRP, seromucoid, positive ANA

Other investigations, consults

- Blood analysis for urogenital infections:

PCR (polymerase chain reaction): **DNA of Ureaplasma urealyticum, Mycoplasma hominis is detected;**

ELISA (enzyme-linked immunosorbent assay): **Mycoplasma hominis IgG – 2,623, Ureaplasma urealyticum IgG – 0,941.**

- Microprecipitation test of blood serum for syphilis , HIV test – negative;
- ECG: sinus rhythm with HR - 74, electric axis of the heart – normal position, no pathological changes.
- Consult of orthopedist-surgeon: **right-sided coxarthrosis 3-4degree; persistent severe pain syndrome; hip replacement is recommended.**
- X-ray of cervical spine in lateral flexion: height and structure of intervertebral spaces is not changed, compaction, uneven deflection of the closure plates in the articular joints. Conclusion: **initial signs of spondylarthrosis;**
- X-ray of ankle joints: thickening of the joint capsule, articular cleft not altered.
- X-ray of knee, sacroiliac, hip joints – on the next slides.

X-ray of knee joints

Moderately pronounced uneven joint space narrowing (JSN), subchondral sclerosis, thickening of soft tissues more pronounced on the right.

Conclusion: bilateral gonarthrosis of 2nd degree



X-ray of sacroiliac and hip joints

- Moderately pronounced uneven joint space narrowing (JSN) of the right sacroiliac joint, subchondral sclerosis, marginal erosions of the closure plates;
- hip joints - significant JSN of both joints more pronounced on the right side, subchondral sclerosis, osteophytes, areas of destruction of the head of the right femur.

Conclusion: signs of coxarthrosis

– right-sided – 4 degree, left-sided – 3 degree, right-sided sacroiliitis 2 degree, aseptic necrosis of the head of the right femur. Lateral pelvis tilt.



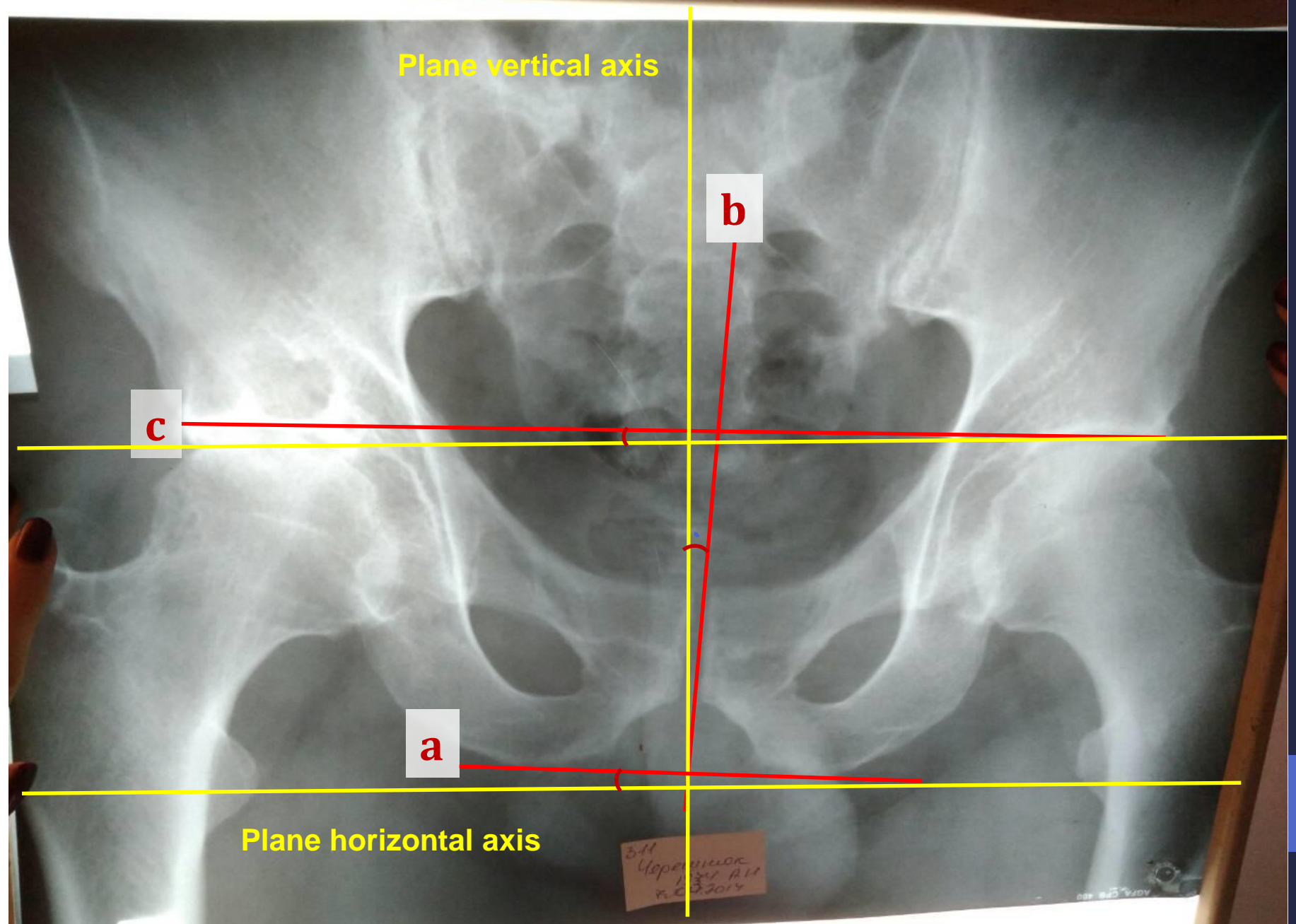
Pelvis tilt

a – horizontal axis
of the pelvis;

b – vertical axis of
the pelvis;

c – line between
roofs of the left and
right acetabulum;

Conclusion: right
lateral pelvis tilt is
present (vertical
axis – $4,5^\circ$,
horizontal axis – 3°)



Diagnosis

Reactive arthritis (since 2010) associated with urogenital infection (ureaplasmosis, mycoplasmosis), chronic continuously-relapsing course, 2nd grade of activity, polyarthritis with knee joints lesions (bilateral gonarthrosis of 2nd degree), ankle joints lesions, hip joints lesions(right-sided coxarthrosis 4th grade, left-sided – 3d grade) , unilateral right-sided sacroileitis 2d grade, functional impairment 2 degree.

Disability 3d degree.

Treatment plan

- Physical activity under the supervision of a physical therapist; avoid overcooling, insolation.
- Metotrexate 10mg per week continuously;
- Folic acid 5mg per day - next day after metotrexate;
- Diclofenac sodium 75mg 2 times per day;
- Methylprednisolone 8mg per day continuously;
- Hondroitine-sulphate 500mg twice daily 1month;
- Calcium and D3 – combined preparation (calcium carbonate 1250 mg, cholecalciferol (vitamin D3) - 10 µg (400 IU)) 1 tab 2 times per day for 2 months;
- Surgical intervention – right hip replacement is recommended.

Conclusion

- In our patient, reactive arthritis was characterized by a chronic persistent course with a constant increase in inflammatory markers and destructive-inflammatory changes in the joints.
- An important role in the progression of reactive arthritis in this patient played multiple bacterial invasions, which were not only a trigger of the onset of the disease, but also maintained a chronicity of the pathological processes.
- This clinical case is an illustration of the fact that infectious bacterial diseases play a key role in the pathogenesis of reactive arthritis, and repeated bacterial infections affect the course and progression of the disease, which leads to a significant disruption of the function of the musculoskeletal system.
- It is important to treat the patient with avoidance of polypharmacy; this goal is achieved by the appointment of several basic drugs and a supportive therapy used in courses.



Thank you for your attention!

Any questions?