Case report

Challenging seronegative arthritis and rheumatic manifestations of syphilis: A case-based review of the great imitator

El-Husseiny PN[1], Abdelrahman W[1], Zayed HS[1], Abd Elmohsen MN[2], Maged LA[1], Gheita TA[1]

[1]Rheumatology Department, Faculty of Medicine, Cairo University, Egypt
[2]Ophthalmology Department, Faculty of Medicine, Cairo University, Egypt

Corresponding author:
Passant N. El-Husseiny, Faculty of Medicine, Cairo University, Egypt.
Email: passantnabil94@gmail.com

Abstract

Syphilis can have varied presentations, including rheumatological and ocular. Early recognition and treatment are necessary to prevent permanent complications. A 34-year-old married male presented with symmetric seronegative arthritis, diagnosed as rheumatoid arthritis, and not responding initially to corticosteroids and Disease-Modifying Anti-Rheumatic Drugs (DMRADs) but eventually resolved. It was followed by amaurosis fugax that lasted for three days. Magnetic Resonance Imaging (MRI) of the brain and spinal cord were normal. Aquaporin-4 antibodies were negative. Anticardiolipin IgM (55 U/ml), IgG (50.8 U/ml) and β-2 glycoprotein-I (68.6 U/ml) were positive, justifying anticoagulation. This was followed by recurrent attacks of diminution of vision and floaters in both eyes; Slit lamp examination and fluorescein angiography revealed posterior uveitis, bilateral vasculitis with leaking discs, cystoid macular edema and peripheral ischemia. He had no orogenital ulcers, lymphadenopathy, skin rashes or sicca manifestations. A serological panel of investigations for infection revealed positive Rapid Plasma Regain (RPR) (1:128), Venereal Disease Research Laboratory (VDRL) and Treponema Pallidum Hemagglutination Assay (TPHA), highly suggestive of syphilis. The patient was treated with ceftriaxone with dramatic improvement. On follow-up, the uveitis resolved with persistent peripheral ischemia, Optic Coherence Tomography (OCT) revealed bilateral dry macula, the serology and antiphospholipids dropped and tended to normalize.

Syphilis may atypically present with symmetrical seronegative polyarthritis, posterior uveitis, retinal vasculitis, optic neuritis and associated positive antiphospholipid antibodies. This case contributes to increase the awareness of rheumatologists and ophthalmologists regarding the confusing clinical aspects of this great mimicking disease, syphilis.

Key words: Syphilis, Seronegative polyarthritis, Uveitis, Retinal vasculitis, Optic neuritis

Introduction

Acquired syphilis in adults is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. The incidence of syphilis has markedly increased over the past decades, with a higher incidence among men and particularly homosexuals[1]. It has been originally known as the 'great mimicker'[2] as it can present with a broad spectrum of diverse clinical manifestations, making the diagnosis difficult especially in atypical presentations.

The Rheumatic Diseases (RD) are heterogenous group of disorders that can have multisystem affection including the musculoskeletal and ocular system. The eye can be compromised in variable presentations in association with RD; in the form of keratoconjunctivitis sicca, cataract, uveitis and scleritis[3]. Optic neuritis which is a demyelinating inflammatory condition has been described commonly in autoimmune diseases as multiple sclerosis and neuromyelitis optica (NMO)[4]. Testing for aquaporin-4 antibodies confers both diagnostic and prognostic values in optic neuritis especially if the brain imaging has no evidence of demyelination[5]. Other differentials for optic neuropathy should be considered including infectious, ischemic, compressive, inflammatory, genetic, metabolic and traumatic causes.

Ocular syphilis is considered to be an early form of neurosyphilis[6]. It can occur in 0.6-2% of syphilis patients at any stage of the disease. It has been known as the great masquerader due to its different presentations as anterior, intermediate, and posterior uveitis (retinitis, retinal vasculitis, choroiditis and placoid chorioretinitis), pan uveitis, scleritis and optic neuropathies[7].

A strong relationship is noted between syphilis and the antiphospholipid (APL) antibodies; in which the APL antibodies were discovered for the first time in the sera of syphilis patients in the early 1900s[8]. It was believed that they interact with the treponemal antigens but it was found that the basis of this positive reaction is the cardiolipin[9]. Therefore, it is expected that syphilitic patients could have positive anticardiolipin antibodies due to cross-reactivity; and similarly, in Anti-Phospholipid Syndrome (APS), biologically false positive syphilitic tests would be expected. Additionally, the Beta-2 Glycoprotein I (β2GPI) antibodies were found to be prevalent in several infectious diseases including syphilis[10].

This work presents a case of syphilis manifesting atypically with seronegative arthritis and uveitis associated with positive APL antibodies. Comparing the case to similar reports is also well thought-out.

Case report

A 34-year-old married male employee presented to the rheumatology clinic with 3 months duration of persistent polyarticular symmetrical arthritis involving the hands and wrists and not associated with morning stiffness. His laboratory tests at that time had revealed a high Erythrocyte Sedimentation Rate (ESR) of 58 mm/1sthour, a high C-Reactive Protein (CRP) of 24mg/L, negative Rheumatoid Factor (RF) and anti-Cyclic Citrullinated Peptide (anti-CCP) antibodies. He was previously diagnosed as a case of seronegative Rheumatoid Arthritis (RA) and had started treatment with prednisone (20mg/day), methotrexate (MTX) IM injections (25mg/week) and sulfasalazine (2gm/day) for 3 months, but he reported no improvement. Two weeks before presenting to the rheumatology clinic, he had received pulse methylprednisolone (500mg/day) intravenously for 3 successive days in addition to intraarticular corticosteroid injection of the right wrist joint. Consent was taken from the patient and the approach was in accordance to institutional ethical standards of Cairo university hospitals and in line with the Declaration of Helsinki.

He had no symptoms suggestive of any systemic connective tissue disorder. He had positive family history of RA. Plain X-ray of both hands revealed no erosions. The patient was fulfilling the 2010 classification criteria for RA[11], justifying the continuation of Disease Modifying Antirheumatic Drugs (DMARDs); MTX (25mg/week), leflunomide (LFN) (20mg/day) and prednisone (20mg/day) while the sulfasalazine was stopped.

One week after presenting to the rheumatology clinic, he had an acute attack of blurred vision (amaurosis fugax) for 3 days in the right eye with spontaneous improvement. He did not report having corona virus disease 2019 (Covid-19) infection and has not received its vaccine. At that time, arthritis eventually resolved. Laboratory investigations of the patient are shown in Table 1.

Table 1: Laboratory investigations of the patient

Parameter	Result
ESR (mm/1st hour)	12
CRP (mg/l)	16.6
CBC parameters	
Haemoglobin (gm/dl)	14.8
WBCs ˣ10³(cell/mm³)	6.8
Platelets ˣ10³(cell/mm³)	285
Creatinine (mg/dl)	1.4
Urea (mg/dl)	20
ALT (U/l)	22
AST (U/l)	13
INR	0.9
Autoimmune profile	
RF	Negative
Anti-CCP	Negative
ANA	Negative
Anti ds-DNA	Negative (<1/10)
C3 (complement)	132
C4 (complement)	29
Extractable nuclear antigens	Negative
Antiphospholipid profile	
Anti-cardiolipin IgM (U/ml)	Positive (55)
Anti-cardiolipin IgG (U/ml)	Positive (50.8)
Anti-β2GPI IgM (U/ml)	Negative (3.1)
Anti-β2GPI IgG (U/ml)	Positive (68.6)
LAC (dRVVT screen ratio)	Negative (1.1)
Panel of infections	
Tuberculin test	Negative
HIV antibody	Negative
HSV IgM	Negative
HSV IgG	Negative
Hepatitis B-surface antigen	Negative
Hepatitis B-core total	Negative
Hepatitis C antibody	Negative
ACE	Negative
Antistreptolysin O Titer	Negative (<200)
Serum syphilis screen	
RPR	Positive (1:128)
VDRL (qualitative)	Reactive
TPHA	Positive

ESR; Erythrocyte sedimentation rate; CRP: C-reactive protein; CBC: Complete blood count; WBC: White blood cell, ALT: Alanine transaminase; AST: Aspartate transaminase, INR: International normalized ratio; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; ANA: Anti-nuclear; ds-DNA: anti-double stranded DNA; DNA: Deoxyribonucleic acid; Anti-β2GPI: Anti-β2 glycoprotein I, LAC: Lupus anticoagulant; dRVVT: diluted Russell Viper Venom Time; HIV: Human immunodeficiency; HSV: Herpes simplex virus; ACE: Angiotensin converting enzyme; RPR; Rapid plasma reagin; VDRL: Venereal Disease Research Laboratory; TPHA: Treponema pallidum hemagglutination assay.

Table 2: Reported cases of syphilis presenting with arthritis

	USA [17]	USA [18]	UK [19]	France [20]	China [21]	Brazil [22]	Singapore [23]	USA [24]	Morocco [25]	USA [26]	Egypt *(this case)*
Year	1979	1987	2008	2009	2012	2013	2017	2021	2022	2023	2023
Age	(n=7) 20-44	53	27	48	69	19	46	31	74	61	34
Gender	5 F/ 2 M	F	M	M	M	M	M	M	M	M	M
Arthritis	Oligo	Poly	Mono	Oligo	Mono	-	Poly	Poly	Mono	Mono	Poly
Joints	(hand/ knee/ ankle/ SCJ)	(knee/ wrist/ shoulder/ elbow)	(knee)	(knee/ elbow)	(knee)		(hand/wrist/ elbow/knee/ ankle)	(hand/ wrist)	(knee)	(ankle)	(hand/ wrist)
Arthralgia	-	-	-	-	-	(knee/SIJ/ elbow)	-	(hand/ wrist/ elbow)	-	(general -ized)	
Ocular	Absent	Absent	Absent	Absent	Absent	Panuveitis	Conjunct -ivitis	Panuveitis	Absent	-	Post. uveitis ON, RV
Muco-cutaneous	Papules Plaques	Maculo papular	Pustules	Maculo papular	Plaques	Keratoderma, erythema, onycho-dystrophy	Erythrema maculopapular plaques hyperpigment	Absent	Papules		absent
Constit -utional	Fever/LNs	Fever/ wt loss/ anorexia	Absent	LNs	Fever/ wt loss	-	LNs	Absent	Absent	Wt Loss	Absent
Others	TS	DM/ hepatitis					oncholysis		Pneumonia		
L puncture	-	Done	-	-	-	-	-	Done	-		-
Syphilis serum screen	(1):VDRL: 1/64-1/1512	RPR: 1/256 TPHA: +ve	IgM EIA: -ve *then* +ve	VDRL: 1/64 TPHA: +ve	RPR:1/16 TPHA:+ve	VDRL:1/128	RPR: 1/256 IgG EIA:+ve	RPR: 1/32 TPHA: +ve	VDRL:1/32 TPHA: +ve		RPR:1/128 VDRL: +ve TPHA: +ve
Autoimmune profile	Not done	ANA: 1/50 (speckled)	RF: -ve ANA: -ve	RF: -ve ANA: -ve ANCA: -ve C3/C4: normal	RF: -ve ANA: -ve ANCA: -ve			RF: -ve ANA: -ve HLA-B27:-ve Anti-CCP:+ve	RF: -ve ANA: -ve ANCA: -ve Anti-CCP: -ve		RF: -ve ANA: -ve Anti-CCP:-ve antiDNA:-ve C3/C4: normal ENA: -ve
APLs	-	-	-	-	-	-	-	-	-	-	ACL/ antiβ2GPI IgG: +ve

SCJ: Sternoclavicular joint; SIJ: Sacroiliac joint; ON: Optic neuritis; RV: Retinal vasculitis; LNs: Lymph nodes; TS: Tenosynovitis; VDRL: Venereal Disease Research Laboratory; RPR: Rapid plasma regain; EIA: Enzyme immunoassay; TPHA: Treponema pallidum haemagglutination assay; ANA: Anti-nuclear; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; ANCA: Anti-neutrophil cytoplasmic antibody; Anti-ds DNA: Anti-double stranded DNA; ENA: Extractable nuclear antigen; APL: Anti-phospholipid antibodies; ACL: Anticardiolipin; Anti-β2GPI: Anti-β2 glycoprotein; LAC: Lupus anticoagulant

Table 3: Cases of syphilis associated with antiphospholipid antibodies

	USA [31]	UK [32]	Egypt *(this case)*
Year	2006	2017	2023
Age	58	38	34
Gender	F	M	M
Articular	Absent	Absent	Polyarthritis (hand/wrist)
Ocular	Absent	Absent	Posterior uveitis, ON, RV
Mucocutaneous	Absent	Absent	Absent
Constitutional	Absent	Absent	Absent
Others	PBC	Seizure Brain infarction	Absent
L puncture	Not done	Done	Not done
Syphilis serum screen	VDRL: +ve FTA-ABS: +ve	RPR: 1/16 TPPA: 1/1280 Treponemal IgM: +ve	RPR:1/128 VDRL: +ve TPHA: +ve
Autoimmune profile	RF: -ve AMA (M2 type): +ve	ANCA: -ve	RF: -ve ANA: -ve Anti-CCP: -ve antidsDNA:-ve C3/C4: normal ENA: -ve
APLs	ACL: +ve LAC: +ve	ACL: +ve LAC: +ve	ACL: +ve antiβ2GPI IgG: +ve LAC: -ve

ON: Optic neuritis; RV: Retinal vasculitis; PBC: Primary biliary cirrhosis; VDRL: Venereal Disease Research Laboratory; RPR: Rapid plasma regain; TPPA: Treponemal pallidum particle agglutination; TPHA: Treponema pallidum haemagglutination assay; FTA-ABS: Fluorescent treponemal antibody absorption assay; ANA: Anti-nuclear; RF: Rheumatoid factor; AMA: Antimitochondrial; Anti-CCP: Anti-cyclic citrullinated peptide; ANCA: Anti-neutrophil cytoplasmic antibody; Anti-ds DNA: Anti-double stranded DNA; APL: Anti-phospholipid antibodies; ACL: Anticardiolipin; Anti-β2GPI: Anti-β2 glycoprotein; LAC: Lupus anticoagulant; dRVVT: Direct Russsell Viper Venom Time

The Visual Evoked Potential (VEP) was normal and Magnetic Resonance Imaging (MRI) of brain and cervical spine were free and showed no demyelinating lesions. MTX and LFN were stopped and steroids were tapered gradually until finally stopped. Positive APL antibodies justified providing anticoagulation. The patient was kept on warfarin 9 mg/day and aspirin 75mg twice daily. The International Normalized Ratio (INR) was 2.7. Although APS is a disease characterized with thrombosis, APL antibodies may be associated with non-criteria manifestations including neurological and ocular[12].

Four months later, the patient presented with recurrent attacks of diminution of vision and floaters in both eyes. On eye examination, he had mild afferent pupillary defect in the left eye, best corrected visual acuity was 80% (right) and 60% (left), 0.5+ of anterior chamber cells,vitreous cells and haze bilaterally, blunt foveal reflex and bilateral hyperemic disc nasally. His fluorescein angiography revealed bilateral vasculitis with leaking discs, cystoid macular edema and peripheral ischemia (Figure 1), the Optical Coherence Tomography (OCT) showed bilateral mild parafoveal macular edema and left irregularity of retinal pigment epithelium with overlying loss of normal photoreceptor line (Figure 2). A serological panel of investigations for infection was done to rule out infectious causes of optic neuropathy and posterior uveitis (Table 1).

Figure 1: Pre-treatment and post-treatment imaging. On the left; Fluorescein angiography showing bilateral posterior uveitis with cystoid macular edema. On the right; Fluorescein angiography consistent with resolved posterior uveitis and peripheral ischemia

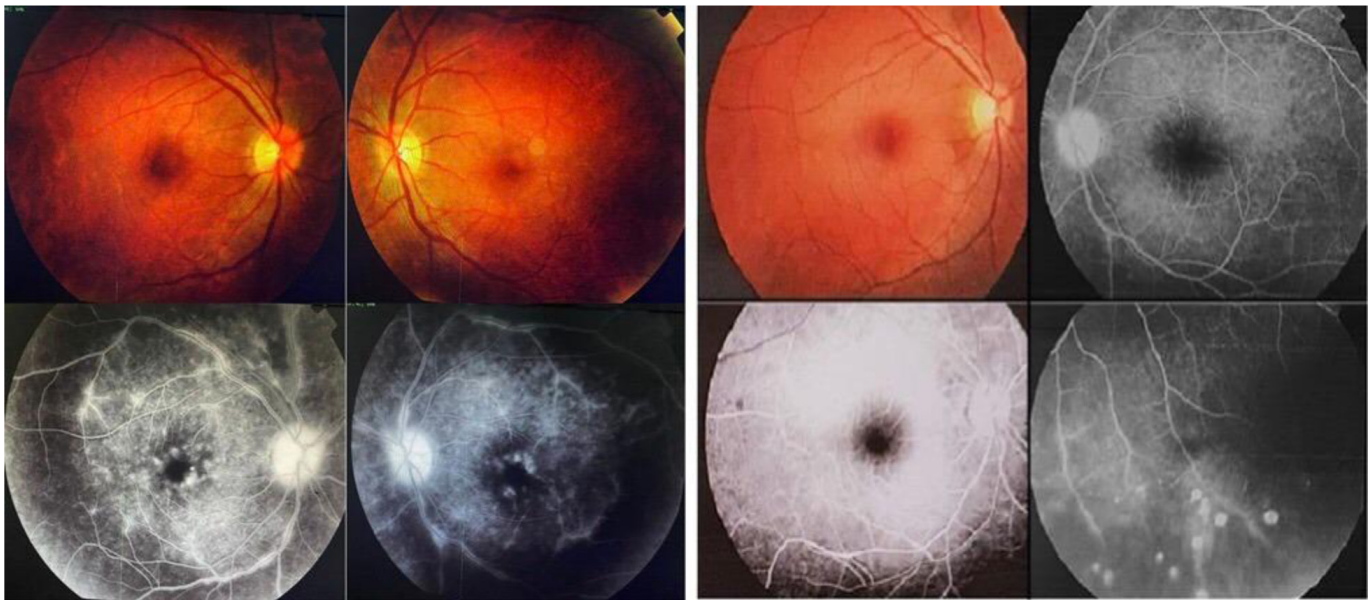
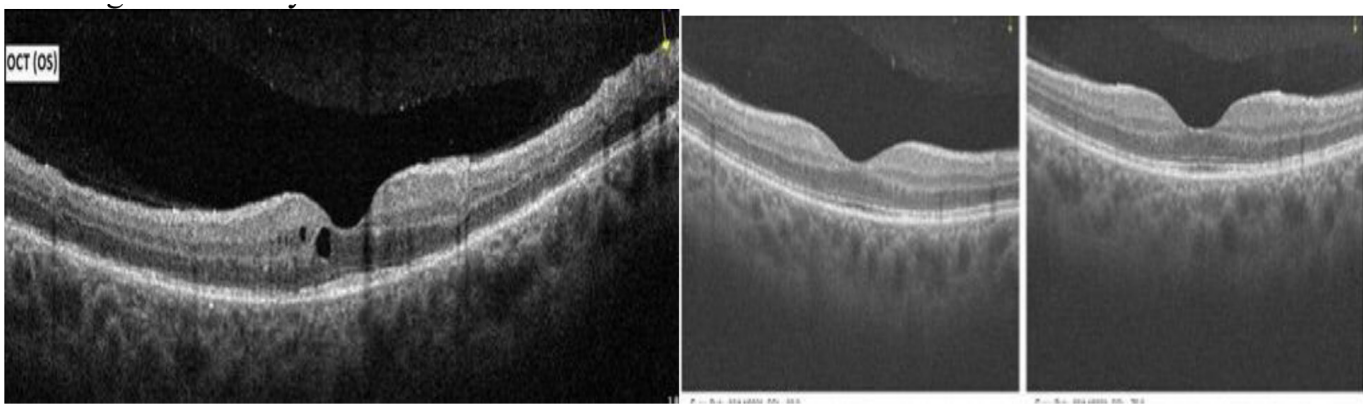


Figure 2: Pre-treatment and post-treatment imaging. On the left; Left eye OCT (optical coherence tomography) showing mild parafoveal macular edema and irregularity of the retinal pigment epithelium with overlying loss of the normal photoreceptor structure. On the right; OCT showing bilateral dry macula



A final diagnosis of posterior uveitis secondary to syphilis was reached; as for the arthritis, it was considered to be a self- limiting manifestation of secondary syphilis associated with syphilis- induced APL antibodies. The patient did not recall having genital ulcers or history of sexually transmitted disease but he did not deny unsafe sexual behavior. His partner was also examined for syphilis and was found to be negative. Warfarin and aspirin were both stopped. The patient was kept on ceftriaxone 2gm IM daily for 2 consecutive weeks, according to the Centers for Disease Control (CDC) and prevention guidelines[13] and the European International Union against Sexually Transmitted Infections[14]. The patient's visual acuity improved dramatically and he did not experience further attacks of diminution of vision. The RPR test was repeated and its titer had declined to 1:64 after 3 months and to 1:32 after 6 months.

The APL profile was repeated 12 weeks after treatment with a remarkable drop in the anticardiolipin IgM (8.2 U/ml) and IgG (25.7 U/ml), the β2GPI IgM and LAC were negative, but the β2GPI IgG was still positive with a significant titer at 76.7 U/ml. Provided those findings, the patient was kept on aspirin with close follow-up.

After 6 months, the unaided visual acuity was 100% (right) and 90% (left). At the last follow-up, fluorescein angiography revealed resolution of vasculitis and macular edema with persistent capillary dropout and retinal ischemia (Figure 1); and the OCT revealed bilateral dry macula (Figure 2).

Discussion

Musculoskeletal manifestations in secondary syphilis include osteitis, periostitis and synovitis usually presenting as polyarthritis, sometimes as oligoarthritis predominantly affecting the knees[15]. Moreover, spondylitis and sacroiliitis have been described[16]. It should be noted that arthritis in secondary syphilis is rare occurring in 4-8% of affected individuals[15]. In tertiary syphilis, joint involvement is as rare and can be in the form of chronic arthritis involving the large joints mainly the knees, however, the most common pattern is known as tabetic arthropathy, which is attributed to the neurological affection in syphilitic patients[15]. Reported cases of syphilis presenting with arthritis[17-26] are shown in Table 2.

Syphilitic uveitis is an infectious uveitis and should be included in the differential diagnosis of any form of ocular inflammation. If unrecognized or mistreated as a non infectious ocular inflammation, it can result in loss of vision[27].

Diagnosis of syphilis is based upon serological tests including non-specific screening tests like VDRL and RPR tests and specific treponemal tests which include Fluorescent Treponemal Antibody Absorption Assay (FTA-ABS), TPHA and Treponema Pallidum Particle Agglutination (TPPA) tests. The World Health Organization necessitates combination of both one of the non-treponemal tests (RPR ad VDRL) and a specific treponemal test for the diagnosis of syphilis[28]. The current case received ceftriaxone 2 gm IM daily for 2 consecutive weeks as he declined hospital admission. Ocular syphilis is considered a part of neurosyphilis and should be treated with IV penicillin but nowadays several antibiotics have been approved for treatment of ocular syphilis including ceftriaxone with the advantage that it can be administrated without the need for hospitalization[13,14]. A lumbar puncture was not done in the present case. In isolated ocular syphilis associated with reactive serology and confirmed ocular abnormalities, the Cerebrospinal Fluid (CSF) examination is not mandatory before starting treatment as long as no associated cranial nerve dysfunction or other neurological abnormalities are found[13].

Antiphospholipid antibodies can occur temporarily in the setting of several infections [29]; syphilis being the first recognized[30]. However, syphilis associated with thrombosis is very rare. In this context, reported cases of syphilis associated with APL antibodies[31,32] are shown in Table 3. Similarly, cross-reactivity of the APL antibodies with Covid-19 infection has been described[29]. However, the APL antibodies profile was different on comparing patients with APS and those with infections including Covid-19; in which higher rates of positive LAC testing, anti-cardiolipin and anti-β2GPI antibodies in patients with overt APS were reported versus those with Covid-19 and other infections. Additionally, higher rates of double and triple positive testing were reported with APS versus with Covid-19 and other infections[29].

In the present case, however, the diagnosis of APS was not made as the patient had no evidence of thrombosis on examination or imaging (fluorescein angiography) accordingly, not fulfilling the classification criteria[33]. Moreover, he developed new symptoms in spite of proper anticoagulation; therefore, positivity of the APL antibodies was interpreted as cross-reactivity. In the present case, the anticardiolipin antibody levels dropped significantly after treatment although antiβ2GPI IgG remained elevated. Low dose aspirin may prevent thrombosis[34].

The diagnosis of syphilis in the present case was made on serological and clinical grounds after exclusion of autoimmune diseases, demyelinating conditions and other infections. The differential diagnoses for the current case included seronegative spondyloarthritis (SpA) such as reactive, psoriatic and enteropathic arthritides as well as Behçet's disease as all can present with peripheral arthritis and uveitis. However, SpA typically present with asymmetrical oligoarthritis. Additionally, the patient had no history of orogenital ulcers, rashes, dactylitis, enthesitis or Inflammatory Bowel Disease (IBD). He also had no family history suggestive of IBD or psoriasis.

Syphilis passes through the following stages: primary, secondary, latent and late symptomatic stage which is known as tertiary syphilis[35]. It can present with heterogeneous manifestations including skin, musculoskeletal and ocular. It is possible that the patient was passing from the secondary stage to early tertiary syphilis owing to the self-limiting course of arthritis which is in-keeping with the natural history of secondary syphilis[36]. A diagnostic dilemma may however exist with seronegative RA in view of the fulfilled classification criteria, positive family history and late response to DMARDs. This highlights the limited practical value of the classification criteria in excluding other diseases with overlapping features and implies that refining the criteria still needs to be considered and is imperative in making proper clinical decisions.

In conclusion, this case reveals the value of considering arthritis, uveitis, retinal vasculitis, optic neuritis and positive APL antibodies in the context of syphilis infection. It should raise the awareness of rheumatologists and ophthalmologists regarding the often-unusual manifestations of syphilis, which should be considered amongst the differential diagnoses of patients with multisystem diseases. Given that syphilis is a curable disease in its early stages, it is essential to timely diagnose and treat it.

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