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CASE REPORT

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A case of syphilis presenting with prolonged etiology-unrevealed fever, accompanying activated partial thromboplastin time prolongation

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Abstract

A 58-year-old woman presenting with 3-week-prolonged fever was referred to our department. Her present history and physical examination results were unremarkable. Her activated partial thromboplastin time (APTT) was prolonged. Upon further investigation, anticardiolipin/beta2-glycoprotein I complex antibodies (CL-β2GPI) were detected, occasionally associated with syphilis. On day 14 of her fourth visit as an outpatient, serological tests confirmed the diagnosis, with newly appeared roseola on her palms and soles. She was in the transitional phase to secondary syphilis. Four months later, after successful treatment, her APTT was normalized with CL-β2GPI negative. Syphilis should be considered in patients with APTT prolongation.

KEYWORDS

activated partial thromboplastin time prolongation, anticardiolipin/beta2-glycoprotein I, syphilis

1 | INTRODUCTION

Typical lesions of primary syphilis spontaneously disappear in a few weeks. With some window period, secondary syphilis presents a variety of symptoms; diagnosing secondary syphilis is sometimes difficult, and patients can be referred to physicians in general medicine. As symptoms of secondary syphilis subside spontaneously, syphilis reaches an early latent stage with infectious potential. Subsequently, physicians should be reminded of syphilis while the patients present with any symptoms.

2 | CASE

A 58-year-old woman with no significant medical history was referred to our department on day X. From day X − 60, she felt "dull" and reported a low-grade fever every few days. She reported having the same sexual partner for several years. After consultation with a gynecologist, screening tests for HIV, HBV, chlamydial infection, and gonococcal infection were performed, and the results were negative. On day X − 20, remittent fever occurred, and her family physician treated her with loxoprofen for a common cold. On day X − 7, she visited her family physician again, but observed no improvement. Blood tests revealed elevated levels of C-reactive protein (CRP) and alkaline phosphatase with normal complete blood cell (WBC) counts and without abnormality on chest X-ray; she was referred to our department. From day X-3, she had dry coughs with chills.

Life history revealed that she managed a nursing home. She delivered twice, but never experienced abortions. Loxoprofen was her only current medication.

She had no episode of appetite loss, weight loss, hemorrhagic state, musculoskeletal symptoms, visiting or staying abroad, tick bite, contact with anyone sick, or contact with animals.

Slight pretibial edema appeared 1 week previously, and other physical findings were unremarkable, especially in superficial lymph nodes, oral cavity, and skins.

TABLE 1 Transition of laboratory data series of each visit, and screening tests performed on day X

			Value				Data checked on day X			
Day	Reference range	Unit	Day X − 7	Day X	Day X + 3	Day X + 119	ESR 1H	3-15	mm	68
WBC	3.5-9.7	$\times 10^9$/L	6.6	7.4	6.4	4.5	TSH	0.35-3.73	μU/L	4.53
Hb	11.2-15.2	g/L	115	105	104	121	FT3	2.2-4.1	pg/mL	2.75
Plt	14.0-37.9	$\times 10^9$/L	36.2	32.1	38.2	26.1	FT4	0.88-1.81	ng/mL	1.14
PT	10.8-13.5	s		12.3			Urinalysis			
APTT	25-38	s		48.2	48.6	29.8	Gravity	1.016		
D-dimer	0-1.0	μg/mL		1.9	1.4		Protein	(–)		
TP	6.5-8.2	g/dL	7.1	6.8			OB	(–)		
Alb	3.7-5.5	g/dL		3.4	3.5		WBC	1-4/HPF		
TB	0.3-1.2	mg/dL		0.36			Antinuclear antibodies			<40
AST	10-40	U/L	21	21	24		Anti-DNA antibodies			<1.0
ALT	5-45	U/L	26	26	27		Anti-Sm antibodies			<1.0
ALP	104-338	U/L	472	420	351	242	Anti-Ro/SSA antibodies			<1.0
γ-GTP	<48	U/L	303	243	175	45	Anti-La/SSB antibodies			<1.0
LDH	120-245	U/L	174	160	181		PR3-ANCA			<0.5
CRP	<0.3	mg/dL	4.65	5.68	1.51		MPO-ANCA			<0.5
Ferritin	6.2-138	ng/dL		172			IGRA			Negative
CL-β2GPI	<3.5	U/mL		20.4		<1.2	Factor VIII		67%-165%	165%
							Factor IX		62%-150%	133%

Alb, albumin; ALP alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CL-β2GPI, anticardiolipin/beta2-glycoprotein I complex antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FT3, free triiodothyronine; FT4, free thyroxine; IGRA, interferon-gamma release assay; LDH, lactate dehydrogenase; RBC, red blood cell; TP, total protein; TSH, thyroid-stimulating hormone; WBC, white blood cell.

To rule out deep vein thrombosis, coagulation tests were performed, and the results are shown in Table 1. Renal function and electrolyte levels were normal. Activated partial thromboplastin time (APTT) was prolonged. Cross-mixing tests showed an inhibitory pattern (Figure 1), which is sometimes observed in antiphospholipid syndrome (APS). Anticardiolipin/beta2-glycoprotein I complex antibodies (CL-β2GPI) were checked and found positive at 20.4 U/mL (reference range: <3.5 U/mL). Electrocardiogram results were within normal limits. Whole-body computed tomography revealed pneumonia (Figure 1), with no swollen lymph nodes or hepatosplenomegaly.

Without sputum and any fluctuation in WBC and CRP levels, she was diagnosed with atypical pneumonia, which seemed partially responsible for CRP elevation, but unrelated to the 3-week-prolonged fever. She was treated with azithromycin (2 g orally as a single dose), without pathogenic tests. On recovery, she was followed up as an outpatient.

She returned on day X + 3, with both ankles painfully swollen and worsened edema, which was orthopedically diagnosed with arthritis. Respiratory symptoms resolved soon after azithromycin administration, and the fever resolved, the reason of which was uncertain. She had stopped taking loxoprofen. Laboratory tests revealed that CRP levels decreased. The emergence of arthritis indicated that the underlying disorder was unresolved, and arthritis worsened after stopping loxoprofen.

Ultrasonography detected no deep vein thrombosis or abnormalities in the liver, spleen, or kidneys. Transthoracic echocardiography found no valvular diseases or vegetations. Her presentation remained unchanged for a week.

As syphilis can cause CL-β2GPI positivity, on day X + 14, rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination (TPHA) tests were performed, which revealed 213 R.U. and 1:2560, respectively.

Concurrently, roseola appeared on her palms, soles, and lower extremities. Thus, secondary syphilis was diagnosed.

On further consideration of her medical history, it was revealed that her sexual partner had primary syphilis on day X − 90; she was negative for syphilis on gynecologist consultation. On day X − 54, she noticed genital blister lesions, which disappeared spontaneously in a few weeks. Prolonged fever was assumed to be a symptom of secondary syphilis, which resolved in the natural course around day X.

In response to amoxicillin administration, all symptoms completely resolved within 2 weeks; biliary enzyme elevation and arthritis, caused by syphilis, improved, and pretibial edema might be

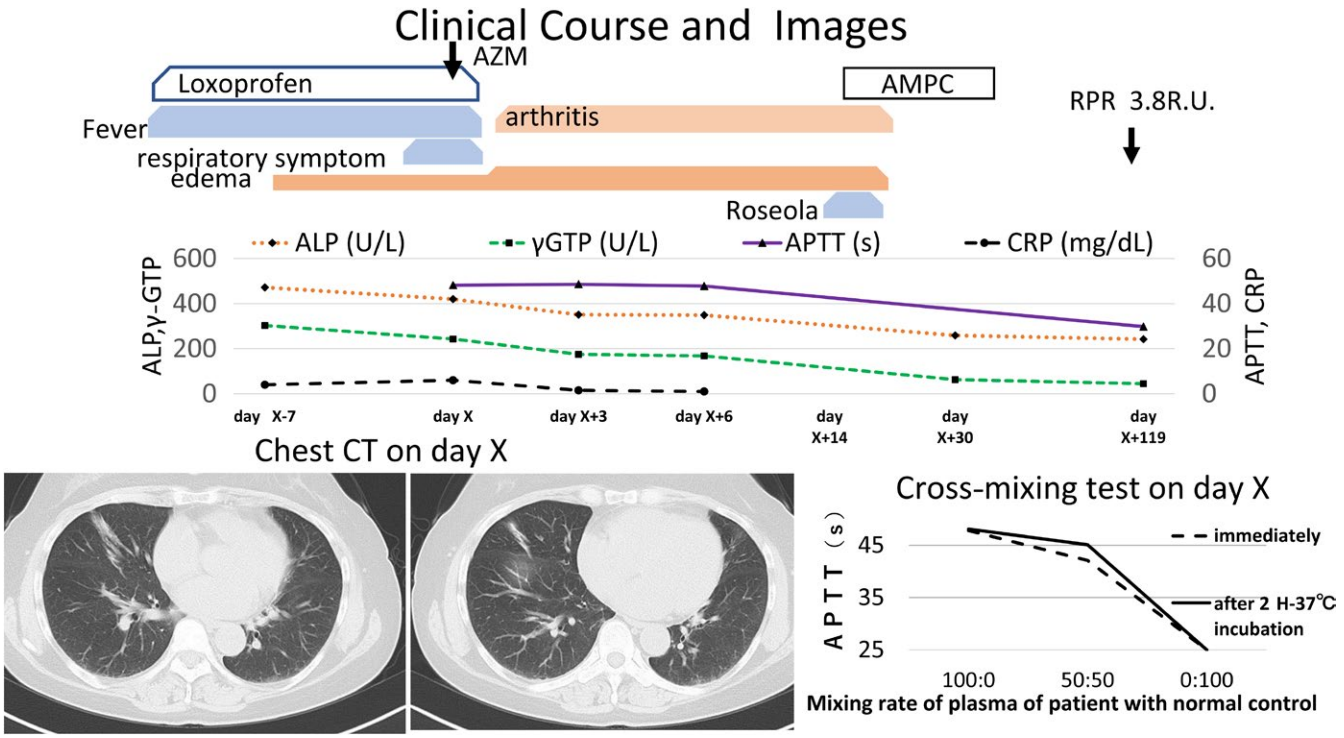

FIGURE 1 Clinical course and images. Pneumonia was detected on chest CT on day X, which was not seen on the chest x-ray of the patient on day X − 7. Cross-mixing tests show an upward convex curve, which indicates the existence of coagulation inhibitor. Clinical course and medication of the present patient are shown with transition of laboratory data series of each visit day. The main problem of the patient was initially prolonged fever. Atypical pneumonia was detected on day X, which emerged around day X − 3; the patient was effectively treated with azithromycin. The fever resolved soon after azithromycin administration. Consequently, arthritis emerged on the lower legs, and pretibial edema worsened. Around day X + 14, roseola appeared on the patient's hands, soles, and lower legs. The patient was diagnosed with syphilis and treated with amoxicillin; all the symptoms accompanying syphilis resolved within two weeks. Prolongation of APTT was detected on day X, the first visit to our department. Elevated levels of ALP and γ-GTP were previously detected, which stayed above the normal limit. CRP elevation seems to be accelerated by pneumonia, which decreased to 1.51 mg/dL after azithromycin administration, but persisted thereafter. All the parameters on the graph returned to normal after amoxicillin administration. AZM, azithromycin; AMPC, amoxicillin; RPR, rapid plasma reagin test; APTT, activated partial thromboplastin time; ALP, alkaline phosphatase; CRP, C-reactive protein

a symptom of syphilitic periostitis (Figure 1). On day 119, APTT returned to normal and CL-β2GPI was not detected.

3 | DISCUSSION

Activated partial thromboplastin time prolongation with normal prothrombin time indicates the existence of coagulation inhibitor or coagulation factor deficiency; differential diagnosis is confirmed with cross-mixing tests. Coagulation inhibitor creates an upward convex curve (Figure 1).[1] Lupus anticoagulant (LA), one of the diagnostic criteria for APS, is confirmed by adding excessive phospholipids to a patient's plasma, which normalizes APTT. Unfortunately, this confirmation test was not done.

Cardiolipin is a phospholipid extracted from bovine heart. RPR detects anticardiolipin antibodies; *T. pallidum* shares the same epitope with cardiolipin.

Antibodies that react with phospholipids are called antiphospholipid antibodies (APL).[2,3] APL can cause thrombosis, also known as APS; one of the target molecules of thrombotic APL was revealed to be β2GPI in the cardiolipin assay. This type of APL is called CL-β2GPI. As thrombotic APL reacts with cardiolipin, this can result in a "biological false positive (BFP)." CL-β2GPI can be associated with LA activity,[1] but the relationship between CL-β2GPI and APTT prolongation has not been investigated.

The prevalence of CL-β2GPI varies from 4% to 10% in syphilis.[2–4] Thus, patients with syphilis can present with CL-β2GPI-associated APTT prolongation. LA is reported in patients with syphilis, especially in the second stage. Screening for "BFP" should have been considered at initial practice. Generally, CL-β2GPI in syphilis is not associated with thrombosis.[5,6] In view of the clinical course of this case, there are no other reasons to trigger APTT prolongation except syphilis.

Lung lesions are rare in secondary syphilis.[7] Secondary pulmonary syphilis is defined as radiologically detected lung lesions with no other etiology in patients with confirmed secondary syphilis, which disappeared with successful syphilitic therapy. All symptoms of the present case appeared to be of syphilitic origin. Respiratory symptoms resolved with oral azithromycin. After the appearance of roseola, azithromycin resistance was indicated.[8] Consequently, the

pneumonia seems not to be of syphilitic origin. *Mycoplasma pneumoniae* is a possible alternative cause, although confirmation tests are lacking. *Mycoplasma pneumoniae* can induce CL-β2GPI or LA; the numbers of cases referring to these antibodies are less than 10[5,9]; the prevalence of CL-β2GPI in *M. pneumoniae* infection is too low to be estimated.[5,10] It is reasonable to consider that CL-β2GPI in the present patient was associated with syphilis.

In conclusion, syphilis should be considered in patients with APTT prolongation.

CONFLICT OF INTERESTS

The author has stated explicitly that there are no conflicts of interest in connection with this article.

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