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CASE REPORT

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Challenging in leprosy relapse with antiphospholipid syndrome diagnosis: A case report

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Key Clinical Message

Infectious diseases like leprosy can cause antiphospholipid antibodies, leading to blood clots. Clinicians should consider this for patients with unusual thrombotic events and prior infectious disease history.

Abstract

This case report details the diagnostic challenge of a 42-year-old man with a history of treated leprosy who presented with clinical features suggestive of antiphospholipid syndrome (APS). Vascular angiography revealed thrombosis, and serological tests were positive for APS antibodies. However, the patient subsequently developed symptoms, including thenar atrophy, paresthesia, and hypopigmented skin patches, which prompted further investigation. Electromyography detected sensorimotor polyneuropathy, while a nerve biopsy indicated a resurgence or chronic presence of leprosy. Despite initial APS management, the case evolved into a leprosy relapse confirmation after 20 years of remission, underscoring the diagnostic intricacies when concurrent autoimmune antibodies and infectious disease manifestations are present. This report emphasizes the importance of considering a broad differential diagnosis, including the potential for infectious disease relapse, in the presence of antiphospholipid antibodies. It illustrates the necessity of an interdisciplinary treatment approach in complex clinical scenarios.

KEYWORDS

antiphospholipid syndrome, leprosy, thrombosis, vasculitis

1 | INTRODUCTION

Antiphospholipid antibodies (aPL) are a group of antibodies in autoimmune diseases and infectious diseases.[1] Infection-related aPLs can occur without thromboembolic complications, and the presence of infection can lead to the disappearance of remission.[2] However, it is essential to note that these antibodies have also been reported in various infectious diseases, including HIV, HCV, HBV infections, syphilis, and leprosy. In these diseases, aPL typically does not lead to thrombotic events or manifestations of antiphospholipid syndrome (APS).[3]

Leprosy results from an infection with *Mycobacterium leprae*, principally impacting the nervous system and skin.

Also, it may present with various clinical presentations and rarely mimic autoimmune vasculitis.[4,5] This case report presents a 42-year-old man who was diagnosed with APS before the detection of vasculitis.

2 | CASE HISTORY/EXAMINATION

A 42-year-old male with a previous history of treated leprosy 20 years earlier, asymptomatic for 5 years post-therapy, sought care at the orthopedic clinic. His chief complaints were fatigue, arthralgia, and necrotic ulcers on the pulps of the first and second digits of his left hand. He reported initial paresthesia in the fingertips prior to the onset of ulcers. Over several weeks, this sensory disturbance was succeeded by a purpuric rash, culminating in the formation of the necrotic lesions observed upon presentation. Vascular angiography to assess for possible ischemia and thrombosis revealed tapered digital arteries in the fingers, as mentioned earlier, indicating thrombotic events. Consequently, the patient was referred to the rheumatology clinic to assess the reason for identified thrombosis in an atypical presentation.

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT)

The patient underwent serological testing for anticardiolipin and anti-β2-glycoprotein antibodies on two separate occasions, with an interval of 12 weeks between the tests. Both tests revealed positive results. Thus, a diagnosis of APS was established. The patient was managed with daily doses of 80 mg of aspirin and 5 mg of warfarin.

Approximately 1 month ago, the patient presented at the clinic with complaints of thenar atrophy and paresthesia affecting the left hand. A decreased grip strength in the left hand and hypopigmented patches (Figure 1) on the patient's abdomen and left arm were observed upon physical examination. Electromyography-nerve conduction velocity (EMG-NCV) and a biopsy of the cutaneous patches were subsequently requested. The EMG-NCV findings suggested multifocal mononeuritis, profound axonal peripheral sensorimotor polyneuropathy, and bilaterally entrapment of both medial and ulnar nerves. In addition, the skin biopsy revealed no evidence of acid-fast bacilli. Based on the EMG-NCV findings, the patient was admitted to the rheumatology ward, and several laboratory tests were ordered (as delineated in Table 1). Furthermore, given the clinical suspicion of vasculitis, he commenced treatment with high-dose prednisolone at 1000 mg administered intravenously over 3 days, pending the laboratory results.

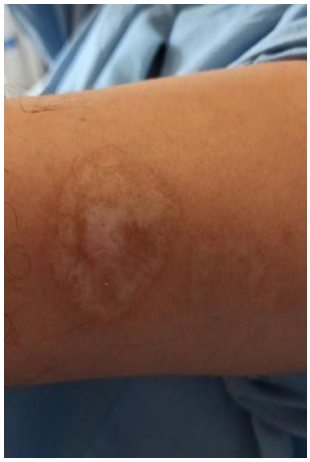

FIGURE 1 Skin patches.

Considering complement levels within normal limits and negative results for perinuclear antineutrophil cytoplasmic antibodies (P-ANCA), cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA), and antinuclear antibodies, the possibility of primary systemic vasculitis and connective tissue disease-associated vasculitis were excluded. Subsequent diagnostic procedures included a sural nerve biopsy, which demonstrated increased infiltration by macrophages and lymphocytes surrounding nerve fibers, a finding consistent with either reactivation or chronic manifestation of leprosy. Based on these findings and the reconfirmation of leprosy, the patient was directed to a dermatologist for the joint management of APS and leprosy to commence appropriate and concurrent treatment modalities.

4 | CONCLUSION AND RESULTS (OUTCOME AND FOLLOW-UP)

Upon consultation with the dermatology specialist concerning a relapse of leprosy, the patient was diagnosed with the paucibacillary form of the disease, which is characterized by a fewer number of lesions and a smaller bacterial load. Considering the clinical manifestation and World Health Organization guidelines for treating paucibacillary leprosy, the patient was prescribed a regimen comprising dapsone, administered at a daily dosage of 100 mg, and rifampin at a monthly dosage of 900 mg. This combination therapy was scheduled for a total period of 9 months.

5 | DISCUSSION

Mycobacterium leprae complex comprises both *M. leprae* and *Mycobacterium lepromatosis*, the causative agents of

TABLE 1 Laboratory parameters of the patient.

Laboratory parameters	Patient's values	Normal range
Leukocyte count, per μL	4.1×10^3 (89.1% Neut, 10.4% Lymph)	$4–10\times10^3$
Hemoglobin, g/dL	14.7	12.3–15.3
Platelet count, per μL	191,000	150,000–450,000
INR, index	4.35	0.9–1.0
PTT, seconds	34	25–45
ESR, mm/h	12	0–30
CRP, mg/L	9	<6
SGOT, g/dL	20	8–35
SGPT, g/dL	14	8–35
Alk.P, U/L	163	64–306
BUN, mg/dL	32	7–20
Creatinine, mg/dL	1	0.5–1.1
ANA, IU/mL	8.1	<12
C-ANCA	0.1	<12
P-ANCA	2.2	<12
Anti-dsDNA, IU/mL	0.5	<1.2
C3, mg/dL	95	90–180
C4, mg/dL	19	10–40
CH50, mg/dL	87	51–150
Lupus anticoagulant	22	20–39
Anticardiolipin (IgM)	157	0–15
Anti-cardiolipin (IgG)	9.1	0–15
Anti-β2-glycoproteins (IgM)	64.8	0–20
Anti-β2-glycoproteins (IgG)	27	0–20
Homocysteine	12	
Cryoglobulins	Negative	
HBsAg	Negative	
HIVAb	Negative	
HCVAb	Negative	

Abbreviations: ANA, antinuclear antibodies; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; C3, component 3; IgM, immunoglobulin M; P-ANCA, perinuclear antineutrophil cytoplasmic antibodies, PTT: Partial thromboplastin time, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, HBsAg: Hepatitis B surface antigen, HIVAb: Human immunodeficiency virus antibody, HCVAb: Hepatitis C antibody.

leprosy, a treatable infectious disease.[6] Clinical manifestations include erythematous or hypopigmented patches associated with reduced or lost sensation. The disease primarily affects the skin, peripheral nerves, and other tissues. The clinical classification of leprosy considers a spectrum, where at one end, paucibacillary or tuberculoid leprosy is found in patients with effective T-cell-mediated immune responses. Such patients exhibit fewer lesions, which typically harbor low numbers of mycobacteria. At the opposite end of the spectrum, multibacillary or lepromatous leprosy is present in patients with poor cell-mediated immunity, characterized by numerous lesions laden with abundant mycobacteria. Between these two poles, unstable, intermediate forms—termed "borderline" leprosy—may shift toward either pole.[6–8] Moreover, the study by Jones et al.[9] described a pediatric case of leprosy concurrent with APS. In contrast, we report a similar adult case, presenting analogous laboratory test results.

An atypical leprosy reaction, known as the Lucio phenomenon (LPh), frequently manifests in patients with multibacillary leprosy. LPh is characterized by necrotizing, vasculitis skin lesions and typically results from the infiltration of macrophages, which are often laden with bacilli, into the vascular structures after infection with *M. leprae* or the recently identified strain, *M. lepromatosis*.[10,11] The clinical presentation of Lucio's

TABLE 2 Association between leprosy and antiphospholipid syndrome (APS): A summary of empirical studies.

Author (year)	Case Summary	Laboratory findings	Treatment	Reference
Jones et al. 2022	A pediatric case where a patient with lepromatous leprosy developed deep vein thrombosis and secondary pediatric APS.	Elevated activated partial thromboplastin time—INR of 1.13—high lupus anticoagulant titers and beta-2-glycoprotein I IgM—negative complement levels (C3 and C4), ANA titers, RA factor, antistreptolysin O (ASO) titers, and aCL antibodies.	The regimen of rifampicin, dapsone, and clofazimine for leprosy—heparin with a pediatric-adjusted dose—Transition to oral anticoagulation with acenocoumarin titrated to maintain an INR of 3.	9
Kumar et al. 2019	A 34-year-old male patient presented with pain and swelling in the back of the left thigh. He also had a history of right hemiparesis with residual weakness, wrist and foot drop, and reduced pinprick and temperature sensations on the dorsum of the right hand.	Low-grade anemia—leucocytosis—raised erythrocyte sedimentation rate (90 mm)—C-reactive protein (3.04 mg/dL)—positive IgG and IgM antibodies for anticardiolipin with titers of 46 and 207, respectively—positive beta 2 glycoprotein-1—Split skin smear positive for *Mycobacterium leprae*.	Dapsone 100 mg, clofazimine 50 mg, rifampicin 600 mg monthly, and prednisolone 30 mg and folic acid 5 mg daily.	21
Guevara et al. 2019	A 32-year-old Indonesian woman presented with a painful blistering rash on the bilateral lower extremities and a fever concerning cellulitis. Examination revealed erythematous swelling of both lower legs, scattered hemorrhagic bullae, petechiae, purpuric macules, and patches on the toes and soles. Skin biopsy results confirmed lepromatous leprosy with the Lucio phenomenon.	Normal white blood cell count—elevated C-reactive protein (2.96 mg/dL) and erythrocyte sedimentation rate (73 mm/h)—positive antinuclear antibody test with a speckled pattern >40×, low C3 (61 mg/dL) and C4 (15 mg/dL) levels—positive test results for lupus anticoagulant, anticardiolipin IgM, and anti-β2-glycoprotein IgG and IgM.	Systemic corticosteroids (methylprednisolone 40 mg intravenous injection every 8 h) and hydroxychloroquine 200 mg twice daily initiated. Anti-leprosy multidrug therapy was administered while continuing the oral steroid.	13
Nunzie et al. 2014	A 76-year-old woman presented with haemorrhagic lesions on her trunk and extremities, along with symptoms such as arthralgia, myalgia, fever, and asthenia. Clinical diagnosis confirmed Lucio's phenomenon with Grade 2 disability.	Normal results for routine laboratory investigations. Positive aCL for IgM. Negative for other autoantibodies. Positive for acute-phase reactants. Histopathology showed signs of long-standing DLL, LPh, and APS.	Administered multidrug therapy for multibacillary leprosy, along with prednisolone and acetylsalicylic acid. The patient was under multidrug therapy without side effects at a 2-month follow-up.	22
Kaliyadan et al. 2009	A 64-year-old male with APS and a history of deep vein thrombosis presented with asymptomatic papules. He had comorbidities, including diabetes, hypertension, coronary artery disease, and dyslipidemia. A dermatological examination revealed infiltrated erythematous papules on the face and trunk and a thickened right common peroneal nerve. A condition suggestive of lepromatous leprosy was confirmed through an AFB smear and skin biopsy.	Positive aCL IgM antibodies, normal routine laboratory investigations, negative serological tests for syphilis, HIV, HCV, and tuberculosis.	Administered multibacillary treatment for leprosy. Due to concomitant anemia and thrombocytopenia, treated with ofloxacin instead of dapsone. Regular follow-up with significant symptomatic improvement observed.	23

Abbreviations: aCL, anticardiolipin antibodies; ANA, antinuclear antibodies; IgM, immunoglobulin M.

phenomenon possesses similarities to those observed in APS, necessitating its consideration as a differential diagnosis where clinical features overlap. This is vital for implementing appropriate therapy and influencing patient prognosis.[12,13]

Guevara et al.[13] represented a patient exhibiting acute fever, lower extremity skin necrosis, and hemorrhagic bullae. Initial laboratory assessments demonstrated positive results for aPL antibodies, prompting treatment initiation with hydroxychloroquine and systemic corticosteroids under a presumptive APS diagnosis. However, the patient's lack of response to therapy necessitated further investigation. Subsequent skin biopsy revealed findings consistent with LPh associated with lepromatous leprosy, including deposition of fibrinogen, complement component 3 (C3), and immunoglobulin M (IgM) within the vasculature, evidential necrotizing vasculitis, copious acid-fast bacilli within histiocytic cells and vascular walls, and clusters of foam cells in perivascular regions. These results led to the definitive diagnosis. The therapeutic regimen was amended to incorporate oral steroids and anti-leprosy medications, which resulted in the improvement of the patient's clinical symptoms. Also, the summary of empirical studies in Table 2 provides evidence of the link between leprosy and APS.

In diagnosing LPh and leprosy with APS, it is necessary to pay attention to the pathogenesis of the disease in the vessels; considering that our patient had an ulcer due to thrombosis, the diagnosis of LPh was ruled out for him during the first hospitalization.

Previous research has illustrated anticardiolipin antibodies in various leprosy clinical forms, with a variable mainly frequency of 20%–98% in lepromatous leprosy. However, tuberculoid leprosy was reported with a 7%–39.5% variable frequency. Additionally, anti-β2-GPI antibody levels in cases with leprosy have been shown to have 2.9%–89% frequency. Unlike other infectious diseases, where these antibodies happen transiently, the previous studies found that these antibodies in leprosy remain persistently positive even years after the therapy ended, which is unclear in our case. The other crucial point is the correlation between thrombotic events and anti-β2 GPI IgG; however, the predominant immunoglobulin isotype is IgM in leprosy patients.[14–16]

In leprosy management, identifying relapse, which involves the emergence of novel active disease manifestations after completion and documented cure with the standard treatment regimen, is crucial.[17] A specific study indicated that the median time to relapse among leprosy patients is approximately 12 years; however, our patient experienced a relapse after an extended period of 20 years.[18] Nerve dysfunction, developing months or years after MDT, may occur independently of overt reactions or relapse, leading to chronic progressive polyneuropathy or multiple mononeuropathies in the absence of active leprosy.[19] It is noteworthy that leprosy relapses can present similarly to vasculitis and other autoimmune connective tissue diseases, potentially complicating the differential diagnosis.[20] In the case presented, the initial diagnosis wavered between vasculitis and leprosy relapse. However, subsequent laboratory investigations enabled us to conclusively eliminate vasculitis, thereby affirming the diagnosis of leprosy relapse.

In conclusion, the presented case report highlights the complicated diagnostic challenges encountered in managing a patient with concurrent leprosy relapse and APS. The persistence of aPL years after leprosy treatment and the potential misdiagnosis with other autoimmune conditions highlight the need for comprehensive interdisciplinary approaches in such complex presentations. The case emphasizes the importance of thorough clinical and laboratory assessments to differentiate between leprosy relapse, vasculitis, and APS, ensuring appropriate management. Furthermore, the extended time gap of 20 years between leprosy treatment and relapse, as well as the atypical clinical manifestations, exemplify the complexities involved in diagnosing and managing such cases. Overall, this case report underscores the necessity for heightened attention and interdisciplinary collaboration to improve outcomes in patients with coexisting leprosy and APS.

AUTHOR CONTRIBUTIONS

Sousan Kolahi: Resources; software; supervision. **Leyla Ghadakchi:** Supervision; visualization. **Amirreza Jabbaripour Sarmadian:** Writing – original draft. **Hamideh Azimi:** Conceptualization; supervision; validation. **Mehdi Jafarpour:** Investigation; resources; writing – review and editing. **Amirreza Khalaji:** Writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this research are available upon reasonable request from the corresponding author.

ETHICS STATEMENT

This study was performed according to the principles outlined by the World Medical Association's Declaration of Helsinki on experimentation involving human subjects, as revised in 2000, and has been approved by the ethics committee of the Tabriz University of Medical Sciences.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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