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Invited Review

Definition and treatment approach of non-criteria clinical manifestations of antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity with persistently positive antiphospholipid antibodies. However, in APS, there are several non-thrombotic clinical manifestations such as thrombocytopenia, cardiac valve disease, microthrombotic nephropathy, skin ulcer, or cognitive dysfunction. These non-criteria manifestations are relatively common and usually are non-responsive to anticoagulation. Among the non-criteria manifestations, thrombocytopenia, skin ulcers, migraine, and heart valve lesions are the most frequent manifestations described in APS. Limited data are available on the treatment of non-criteria manifestations of APS, and most therapeutic options are based on case reports or retrospective non-randomized studies. Although there is no consensus on the treatment of non-criteria manifestations of APS, anticoagulant therapy and immunomodulatory drugs could be combined in most patients.

Keywords: Antiphospholipid syndrome, livedo reticularis, thrombocytopenia, cardiac valve disease, antiphospholipid nephropathy, cognitive dysfunction

Introduction

According to the updated Sapporo classification criteria, antiphospholipid syndrome (APS) is defined as a disease characterized by thrombosis and/or pregnancy morbidity with persistently positive antiphospholipid antibodies (aPL). However, patients with aPL may also experience several non-thrombotic clinical manifestations such as thrombocytopenia, cardiac valve disease, nephropathy, skin ulcer, or cognitive dysfunction, which are collectively known as non-criteria manifestations of APS (1-3). Non-criteria manifestations of APS are relatively common (Table 1), but their accurate prevalence and associated thrombotic risk are unknown. The exact pathogenic mechanism of the occurrence of non-criteria manifestations is still unclear. Usually, these manifestations are non-responsive to anticoagulation, and very few studies address their treatment; there is no consensus on the treatment of these manifestations. Rituximab in APS (RITAPS) is the only therapeutic trial design to evaluate the safety and benefit of rituximab in various non-criteria APS manifestations such as thrombocytopenia, cardiac valve disease, skin ulcer, aPL nephropathy, and/or cognitive dysfunction (4). In this review, we aimed to discuss these non-criteria manifestations and their treatment approaches.

Cutaneous manifestations

Although no skin finding is pathognomonic for APS, cutaneous manifestation can be the initial presentation in approximately 40% of patients with APS, with a similar prevalence in primary APS (31%) and systemic lupus erythematosus (SLE)-related APS (20%) (5-7). The most common skin lesion is livedo reticularis, and skin biopsies show a non-inflammatory thrombosis of the small dermal vessels (5). Livedo reticularis was defined by Miyakis et al. (1) as persistent, irreversible, with rewarming, violaceous, red or blue, and reticular or mottled pattern. Physiological livedo is often seen in upper and lower extremities; however, in APS, livedo also affects the skin of the trunk and buttocks.

Skin ulcers (pyoderma gangrenosum-like or livedoid vasculitis) are usually due to the fibrin deposition within the lumens of superficial dermal vessels and are located in the extremities. These lesions are recurrent and painful, and they can be associated with livedo reticularis or racemosa. Thrombophlebitis, necrotizing vasculitis, subungual splinter hemorrhages, painful skin nodules, cutaneous gangrene, and chronic leg ulcers are other cutaneous lesions (2, 5).

There are successful reports of oral anticoagulation and/or antiplatelet therapy in patients with cutaneous manifestations of APS, but glucocorticoid and immunosuppressive therapies often fail. If the lesions reoc-

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cur or extend despite anticoagulation and/or antiplatelet therapy, other treatments may be added, such as sildenafil, intravenous immunoglobulin (IVIG), recombinant tissue plasminogen activator, plasma exchange, and rituximab (2, 8).

Cardiac manifestations

The heart is one of the major target organs in APS, and the most frequent cardiac manifestations are heart valve lesions such as vegetations and valve dysfunction. Most studies have reported a higher prevalence of valve abnormalities in patients with SLE and aPL by Doppler echocardiography, ranging from 14% to 86%. In primary APS, these have been reported in approximately one-third of patients (1, 9-11). Although the most commonly affected valves are mitral and aortic valves, their significant dysfunction is very rare (10, 12). It is observed that cardiac valve involvement is clinically associated with arterial thrombosis (51% in those with previous arterial thrombosis, 51% with previous venous thrombosis, and 37% with previous obstetric morbidity) and central nervous system manifestations such as ischemia, migraine, and epilepsy in APS (9, 11, 13). Valve vegetations are sterile fibrinous vegetations on the endocardial surface of the valve. Although antithrombotic agents do not stop the progression of valve disease, aspirin or warfarin could be preferred for vegetations associated with a high thromboembolic risk (8, 10). There is no prevention or effective therapy for cardiac valve lesions of APS, and approximately 5% of patients with cardiac valve lesions require valve replacement (2).

Renal manifestations

Renal involvement in APS includes small vessel vaso-occlusive nephropathy defined as APS nephropathy or aPL-associated nephropathy. APS nephropathy is characterized by vascular involvement associated with hypertension, low-grade proteinuria, and acute and/or chronic renal failure (14, 15). Thrombotic microangiopathy was the main intrarenal vascular lesion in the early reported cases of primary and SLE-related APS. Thrombotic microangiopathy is characterized by the presence of fibrin thrombi in the glomeruli and/or renal arterioles, absence of immune complexes and inflammatory cells, and no association with any specific histological class of lupus nephritis (1, 15).

Renal involvement in APS is thought to occur in 3%-40% of patients (16), and renal artery stenosis is the most common renal manifestation, which is seen in 26% of patients with APS. APS nephropathy clinically presents with hypertension, mildly elevated serum creatinine levels, proteinuria, and mild hematuria. Hypertension is the most frequent (approximately 93%) clinical feature described in APS and is frequently an initial sign of underlying renal disease (7, 10). Although routine renal biopsy is not recommended in patients with APS, if there are clinical and laboratory findings that suggest APS nephropathy (new onset of hypertension, proteinuria, hematuria, or renal insufficiency), renal biopsy should be performed to distinguish the thrombotic and inflammatory lesions (9, 14, 15).

APS nephropathy is usually slowly progressive, with no proven treatment. In the presence of microthrombi, the blood pressure control and anticoagulant therapy may improve the renal function. Although there is no consensus on the treatment of APS nephropathy, the patients are usually recommended to take antiplatelet or anticoagulant therapy, together with strict control of arterial hypertension and proteinuria with angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers. In cases with concomitant lupus nephritis, the introduction of immunosuppressive therapy is necessary. However, acute renal failure owing to thrombotic microangiopathy is often treated with plasma exchange. Other therapeutic approaches for refractory cases are IVIG, plasmapheresis, rituximab (anti-CD20), and eculizumab (C5a inhibitor) (8, 10, 14, 15, 17).

Hematological manifestations

Platelets are another class of target cells in APS, and the prevalence of thrombocytopenia has been reported between 20% and 50% (6, 18, 19). In the Euro-Phospholipid Project of 1,000 patients with APS, the frequency of thrombocytopenia was 29.6% (21% in primary APS and 41.9% in secondary APS) (16, 20).

Thrombocytopenia is often mild to moderate (above 50,000 μL^{-1}) and is usually associated with a minimal risk of bleeding (11). In some studies, significant associations among thrombocytopenia and cardiac valve thicken-

Main Points

- The characteristic clinical manifestations of APS are thrombosis and pregnancy morbidity.
- However, there are several non-thrombotic clinical manifestations such as thrombocytopenia, cardiac valve disease, microthrombotic nephropathy, skin ulcer, or cognitive dysfunction.
- There is no consensus on the treatment of non-criteria manifestations.
- Anticoagulant therapy and immunomodulatory drugs could be combined in most patients who have non-criteria manifestations of APS.

Table 1. Most common non-criteria manifestation in APS according to the Euro-Phospholipid Project (16).

Manifestations	Prevalence (%)
Cutaneous manifestations	
Livedo reticularis	24.1
Skin ulcers	5.5
Cardiac manifestations	
Valve thickening/dysfunction	11.6
Vegetations	2.7
Neurological manifestations	
Migraine	20.2
Epilepsy	7.0
Dementia	2.5
Chorea	1.3
Hematological manifestations	
Thrombocytopenia (<100,000/μL^{-1})	29.6
Hemolytic anemia	9.7
Renal manifestations	27

APS: antiphospholipid syndrome.

ing and dysfunction, epilepsy, chorea, arthritis, livedo reticularis, and skin ulcerations were found (6, 21).

Another APS-related hematological manifestation is autoimmune hemolytic anemia with a prevalence of 10% (16). However, in the catastrophic APS, hemolytic anemia is observed in approximately one-third of all cases (10).

APS-related thrombocytopenia is usually mild and does not require any active therapeutic intervention. In the case of severe or symptomatic thrombocytopenia, the management strategy is similar to that in immune thrombocytopenia (ITP), and glucocorticoids with or without IVIG is recommended as the first-line treatment. In patients who are severe and refractory to prednisone therapy, immunosuppressive therapy (azathioprine, cyclophosphamide, and mycophenolate mofetil) could be used as second-line therapy. Rituximab may be effective in patients who are refractory to glucocorticoids and immunosuppressive therapy. Different from ITP, splenectomy should be postponed for as long as possible because of the increased risk of thrombosis for patients with APS who undergo surgery. It is important to keep in mind that the presence of moderate to severe thrombocytopenia in patients with ongoing thromboses is not a contraindication for anticoagulation (8, 17, 22).

Hemolytic anemia is initially treated with glucocorticoids, and second-line therapies include mycophenolate mofetil, cyclophosphamide, and azathioprine. In refractory patients, IVIG and rituximab could be used (8, 17, 22).

Neurological manifestations

Many different neurological manifestations in APS have been reported. Thrombotic manifestations, such as stroke (19.8%), are well known and are responsible for high morbidity and mortality (16). Nonvascular neurological manifestations associated with APS are also associated with a wide range of neurological and psychiatric conditions, including headache, migraine, bipolar disorder, transverse myelitis, dementia, chorea, epileptic seizures, multiple sclerosis-like lesions, psychosis, cognitive impairment, Tourette syndrome, Parkinsonism, dystonia, transient global amnesia, obsessive compulsive disorder, and leukoencephalopathy (11). Some of them, such as migraine (20.2%) or cognitive dysfunction (40%), are frequently described, whereas others are less common (Table 1) (11, 16, 23-25).

Cognitive dysfunction has been consistently reported in patients with APS but is not always associated with APS. Age and livedo reticularis were found to correlate with cognitive dysfunction in APS (25-27). The frequency of dementia was estimated at approximately 0%-6% in aPL positivity and 2.5% in the Euro-Phospholipid Project cohort of 1,000 patients (65% of patients with primary APS versus 35% of patients with secondary APS) (16, 28).

Headache (20%-40%) is the most prevalent neurological symptom reported by patients with APS, and migraine was the most common type. It was reported that history of stroke or transient ischemic attack and lupus anticoagulant positivity are the risk factors for migraine (28, 29). Moreover, migraine is more prevalent among women, and it can be associated with cardiac vegetation (6).

Chorea (1.3%-4.5%) is the most frequent movement disorder described in APS, and patients are more frequently young women, with aβ2GP1 IgM positivity. Besides chorea, various other movement disorders such as dystonia, ballismus, dyskinesia, Parkinson syndrome, and cerebellar ataxia, have been described very rarely in APS (11, 16, 28). In APS, movement disorders are commonly associated with a thrombo-occlusive vasculopathy, often associated with cerebral infarctions and white-matter changes on the brain magnetic resonance imaging (29).

Seizures are commonly reported among the neurological manifestations of APS, and estimated prevalence of seizures is 3.2%-10%. Almost half of the patients develop epilepsy after APS diagnosis (16, 29).

Management of those non-stroke neuropsychiatric manifestations in APS is not yet well established, and it is based on case reports or retrospective non-randomized studies. Some authors recommend low-dose antiplatelet therapy combined with hydroxychloroquine for cognitive dysfunction. In chorea, aspirin or anticoagulant therapy alone or with steroids and haloperidol are commonly prescribed with a good clinical response in most of the patients. Anticonvulsants and anticoagulant therapy could be used in patients with epilepsy. Although non-thrombotic neurological manifestations may benefit from immunomodulation (steroids, IVIG, hydroxychloroquine, and rituximab), most of these manifestations are usually managed with long-term oral anticoagulation (25, 28, 29).

Conclusion

Although APS is defined as a disease characterized by thrombosis and/or pregnancy morbidity, patients with APS may also suffer from several non-thrombotic clinical manifestations; some of them are common. These manifestations are not considered diagnostic for APS. There are not enough data about these non-criteria manifestations, their pathogenic mechanism, and their specific therapeutic approach. Therefore, the management of non-criteria manifestations remains empirical with little evidence. Despite growing evidence of their pathogenic mechanisms being involved in APS, additional studies regarding the clinical course of non-criteria manifestations and therapeutic options are needed.

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