

## The Significance of Anticardiolipin Antibodies in Patients with Vasculitis

*Mary Gantcheva*

*Institute of Experimental Morphology, Pathology and Anthropology with Museum,  
Bulgarian Academy of Science, Sofia, Bulgaria*

\* Corresponding author e-mail: mary\_gant@yahoo.com

We evaluate the incidence of serum anticardiolipin antibodies in patients with different types of vasculitides and vasculopathies and describe clinical, histological and laboratory specificity and disease course in correlation with their positivity. We conclude that they activate endothelial cells in both occlusive and inflammatory vascular diseases, aggravate skin symptoms, but are not related to advanced systemic involvement and poor prognosis. They represent skin ulcerations on acral sites in lupus erythematosus and have a predictive role for thrombosis. Livedo vasculitis may be a clinical sign of antiphospholipid syndrome.

*Key words:* Anticardiolipin antibodies, vasculitis, vasculopathy, antiphospholipid syndrome, livedo vasculitis.

### Introduction

Anticardiolipin antibodies (aCL) are one of the most prominent members of antiphospholipid family. They bind to immobilize cardiolipin in an ELISA and cross-react with phosphatidylserin, phosphatidylinositol, and phosphatidic acid. Their assays are isotype-specific, but of different isotypes: IgG, IgM and IgA. ACL are detectable in up to 2% of the normal population with no definite association with either age or sex. They are revealed also in autoimmune diseases - systemic lupus erythematosus (SLE) and other, infection diseases, malignancies and drug-induced conditions. ACL in patients with autoimmune diseases are completely different from those occurring in patients with nonautoimmune diseases, which confer little risk of thrombosis and are inhibited by cofactor. Autoimmune-related antibodies are suspected to be IgG. They bind with high avidity with high correlation between the presence of aCL and lupus anticoagulant. The pathogenicity of aCL is tend to be due to activation of proinflammatory and procoagulant phenotype sustain by the up-regulation of adhesion molecules, synthesis and secretion of cytokines, chemokines, endothelin-1 and tissue factor [1]. Plasma beta<sub>2</sub>-GPI is always needed to inhibit the contact activation of the intrinsic coagulation pathway, factor XII, factor Xa generating activity, ADP-induced platelet aggregation, and protein C [9].

## Materials and Methods

The total number of 90 patients of both sex aged 18-77 years were enrolled in the study. Several patient groups were differentiated in accordance with the clinical entities: cutaneous necrotizing vasculitis (CNV) – 15 patients, Henoch Schonlein purpura (HSP)-7, Morbus Behcet (MB)-7, cutaneous polyarteritis nodosa (cPAN)–4, systemic lupus erythematosus (SLE) – 25, systemic scleroderma (SSc) – 12, livedoid vasculitis (LiV)–18 and gangrene – 2 (Fig. 1). Antibodies to cardiolipin IgG, IgM, IgA and to beta<sub>2</sub>-GPI IgG were titred by solid-phase enzyme immunoassay on the first visit of each patient. A conformation of aCL-ELISA (chromogenic) positivity in 12 weeks interval was needed. Histology samples were taken with a routine punch 4-mm technique. Clinical observations assessing skin changes and concomitant systemic symptoms were made on the day of the first visit, and at follow-up visits at the end of the first month, sixth month and after one year period.

## Results

Anticardiolipin antibodies were detected in 30 of our patients (**Table 1**).

We found that 4 of the investigated 15 patients with CNV were positive for IgG and IgMaCL. No IgAaCL were detected. One of these cases was a 71-year old man. He developed hemorrhagic, bullous and ulcerative lesions on the skin on his left leg and on the stump of the right one (**Fig. 1**). He was amputated one year before because of thrombosis of a. tibialis posterior dextra. He had high titters of IgGaCL and leucocytoclastic vasculitis on histopathology. We put the diagnosis antiphospholipid syndrome (APS) considering aCL responsible for the thrombosis. We think that vasculopathy has thrombotic origin and vasculitis is concomitant. Another interesting case was that of a young man with wide spread necrosis on the testes and thigh (**Fig. 2**), aCL and leucocytoclastic vasculitis. We achieved improvement with therapy with corticosteroids and anticoagulants. The other two cases with positive aCL and CNV were women who like the previous ones had stormy course of the disease with deep painful bleeding ulcerations.

We had two patients with aCL from our series of 7 patients with HSP (**Fig. 3**), and all of them had only positive IgAaCL, neither IgG nor IgM.

**Table 1.** Clinical entities, number of the investigated patients and number of the positive ones for aCL

Vasculitidis		Vasculopathies
<b>Leucocytoclastic V</b>	<b>Lymphocytic V</b>	
CNV- 15/ <b>4 aCL</b>	SLE- 25/ <b>7 aCL</b>	Livedo vascul- 18/ <b>7 aCL</b>
HSP- 7/ <b>2 aCL</b>	SSc- 12/ <b>4 aCL</b>	Gangrene-2/ <b>1 aCL</b>
M. Behcet- 7/ <b>2 aCL</b>		
cPAN- 4/ <b>3 aCL</b>		



**Fig.1.** Hemorrhagic lesion on the skin of the stump in a patient with CNV and aCL



**Fig.2.** Necrotic ulcer on the skin of the thigh in a patient with CNV and aCL



**Fig.3.** Patient with HSP and aCL



**Fig.4.** Painful nodules and purpuric plaques in a patient with cPAN and aCL

We investigated 7 patients with MB and found that two of them had high titers aCL but only of IgM isotype.

Our patients with elevated aCL with cPAN were three. They had no systemic involvement and therapy with prednisone was successful (**Fig. 4**). The majority of patients with vascular endothelial damage demonstrate aCL with positive correlation between aCL and livedo reticularis.

We observed 7 patients with SLE and positive aCL. This is not uncommon as aCL

are positive in 40% in SLE. All our patients had ulcerations on the extremities and one of them had it on the ear, which is rarely seen.

We tested 12 cases with SSc for aCL and found elevated levels in 4 of them. An amputation of the thumb was required in one patient because of a digital gangrene (**Fig. 5**).

We followed 18 patients with LiV and found that 7 had positive aCL. Two of them developed thromboses years after they had been diagnosed as having LiV (thrombosis of the femoral vein and cerebral thromboembolism). We put the diagnosis APS in 5 of these patients (including the 2 cases above). However, ulcerations and scarring are recognized cutaneous manifestations of aCL and occlusion of the smaller dermal vessels in APS may result in the clinical picture of LiV.

We had 2 other cases with digital gangrene and one of them had high titters of IgGaCL and not reversible ischemic changes (**Fig. 6**). An amputation of the gangrenous digits was necessary. The combination of thrombotic and inflammatory defects compromise tissue perfusion and lead to tissue necrosis.



**Fig.5.** Amputated thumb in a patient with SSc and aCL



**Fig.6.** Gangrenous digits in a patient with positive aCL

## Discussion

Clinical observations showed that high serum levels of aCL aggravates skin symptoms, but are not related to advanced systemic involvement and poor prognosis for our patients with vasculitides and vasculopathies. ACL activate endothelial cells in both occlusive and inflammatory vascular diseases by inducing a proinflammatory and procoagulant phenotype resulting in high thrombogenic activation.

The association of aCL and cutaneous necrotizing vasculitis demonstrates significant tissue ischemia and necrosis (uncommon in vasculitis alone) and lead to dramatic and complicated course of the disease. ACL possibly favor the diminution of blood flow and thrombi form more easily at the site of vasculitis-induced endothelial injury when a coagulopathy exists [3].

The aCL pathogenetic role in Henoch Schonlein purpura is quite controversial. Based on earlier observations it is suggested that aCL are often co-incidentally associated with HSP with no pathogenetic events of occlusive vasculopathy [6]. The presence of IgAaCL may be used as an indicator of adult HSP thus being an indicator of its activity [2]

The frequency of aCL in Morbus Behcet ranges between 8 and 50% in different publications. ACL are pointed as markers of endothelial damage in MB associated with retinal vasculitis [10] and are linked to the risk of development of cutaneous vasculitis and erythema nodosum. According to a study including 128 patients with MB, aCL have not a primary role in MB and regional determinants - environmental or genetic, might also play a role in controlling aCL production [8]. We suppose aCL may cause inflammatory tissue reaction in MB due to acute infection or hypersensitivity to bacterial antigens.

The presence of aCL in systemic lupus erythematosus patients is not uncommon as aCL are positive in 40% in SLE. Having in mind our cases we may say aCL in SLE represent significant tissue ischemia and necrosis with deep skin ulcerations on acral sites. Although vasculitis is not considered to be a common manifestation in systemic sclerosis, it is suggested that vasculitis involving small vessels is present histologically if not always clinically in the SSc patients with severe ischaemia [4]. It is still unclear whether aCL could after a certain period of time lead to vasculopathy or these are the vasculitic changes that lead to the formation of aCL. Or it is possible that aCL in such cases do not have a pathogenetic role but should be interpreted as a marker of vasculopathy. ACL may have a role in the genesis of vascular involvement related to SSc - pulmonary arterial hypertension and digital infarcts.

Livedo vasculitis-like ulcers may be a clinical sign of APS and should raise suspicion for it [7]. We can also speculate of a predictive importance of aCL in LiV for development of thrombosis. It would seem that LiV may represent a clinical sign of a heterogeneous group of diseases that cause an occlusive vasculopathy such as APS or that may occur as a sole entity [5].

## Conclusions

The aCL antibodies are found to activate endothelial cells by inducing a proinflammatory and procoagulant phenotype resulting in high thrombogenic activation in both occlusive and inflammatory vascular diseases. Clinical observations showed that high levels of aCL aggravate skin symptoms, but are not related to advanced systemic involvement and poor prognosis. The presence of IgAaCL may be used as an indicator of adult HSP activity due to their positive correlation with some clinical and laboratory markers of inflammation in the initial phase of the disease. All positive SLE patients represent skin ulcerations and necrosis on acral sites. Occlusion of the smaller dermal vessels in APS may result in the clinical picture of LiV and the suspicions of LiV as a manifestation of APS might be easily adopted.

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