#### CASE REPORT

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# Stroke in a young man with fibromuscular dysplasia of the cranial vessels with anticardiolipin antibodies: a case report

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Abstract A case of fibromuscular dysplasia (FMD), presenting with a non-hemorrhagic infarct is reported. Positivity of anticardiolipin antibodies suggested an immune response. A 40-year-old man presented with sudden onset of stroke, preceded by similar ischemic attacks. Computed tomography (CT) of the brain showed a recent non-hemorrhagic infarct in the left middle cerebral artery (MCA) territory and an old right MCA territory infarct. Serum was positive for anticardiolipin antibodies. These above findings were confirmed at autopsy. A portion of the internal carotid artery and the middle cerebral arteries on both sides revealed features of FMD, with thrombosis. This case suggests an immune mechanism for FMD, hitherto unobserved in the cerebral circulation.

**Key words** Anticardiolipin antibodies • Fibromuscular dysplasia • Stroke in young • Infarct

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# Introduction

Recently, a clinical association between specific neurological disorders leading to ischemic lesions of the brain and the presence of antiphospholipid antibodies has been observed [1-3]. An immune mediated thrombotic tendency produced by these antibodies has been proposed as the pathogenic mechanism of cerebral ischemia and infarction [1]. A high prevalence of these antibodies has been observed in young adults with cerebral ischemia. In a study from south India, serum antiphospholipid antibodies were observed in 23% of stroke patients below 40 years of age, compared to 3.2% in the normal ageand sex-matched controls [4]. A low prevalence of recognized risk factors for stroke and cerebrovascular atherosclerosis has been reported in stroke patients with circulating anticardiolipin antibodies [5]. It is generally felt that this immunovasculopathy results in a noninflammatory luminal occlusion. An association between cerebral vessel damage by fibromuscular dysplasia with vascular occlusion and the concomitant presence of anticardiolipin antibodies has not been reported to the best of our knowledge, although a similar feature has been noted in the renal arteries, based on angiographic studies [6, 7].

We report a case of stroke in a 40-year-old man in whom the neurological events progressed over a period of four years. Limited autopsy study confined to the brain revealed extensive thrombosis of the left internal carotid, middle cerebral and A-1 segments of the anterior cerebral arteries along with features of fibromuscular dysplasia involving the internal carotids and middle cerebral arteries bilaterally.

# **Case report**

# Clinical history

A 40-year-old man presented to the neurological emergency service, with two episodes of generalized tonic clonic seizures, occurring at a 1-week interval followed by altered sensorium. Three years earlier, he had a sudden episode of decreased vision in the left eye, which persisted; he did not seek any medical help for it. About a year later, he had an episode of left hemiparesis along with blurred vision in the right eye. He recovered in a period of six months. He was not known to have diabetes or hypertension. However, he suffered from angina four years prior to the present neurological illness and received treatment for this. There was no previous history of seizures, movement disorders, migraine, deep vein thrombosis, Raynaud's phenomenon or cutaneous vascular lesions. He was a chronic alcoholic and smoker.

On examination, he was febrile and had a pulse rate of 110/min. The rate was regular and was of good volume. All peripheral pulses were normally felt. The blood pressure in the right upper limb in the supine position was 150/110 mmHg. Cardiovascular and respiratory systems were normal. Neurologically he was in altered sensorium, not opening eyes or vocalizing to pain. Had a left gaze preference. The optic fundus revealed optic atrophy on the right and a pale optic disc on the left. There was pupillary asymmetry, the right being 6 mm in diameter, sluggishly reacting, while the left was 4 mm, normally reacting to light. He had a left upper motor neuron facial paresis. The muscle tone of the limbs was spastic on the left side and decreased on the right. He moved the left-sided limbs to pain. The deep tendon reflexes were brisk on the left and sluggish on the right; the planter responses were extensor bilaterally.

In view of recurrent episodes of hemiplegia, in association with blindness and cardiac angina, the possibilities of antiphospholipid syndrome with recurrent ischemic attacks, CNS vasculitis or meningovascular syphilis were considered and investigated. The routine hematological and serological parameters were as follows: hemoglobin, 13 gm/dl; packed cell volume (PCV), 42%; erythrocyte sedimentation rate (Westergren), 8 mm/h; total leukocyte count, 15700/dl; differential count, 95% polymorphs and 5% lymphocytes; platelets, 1.93 x 10 5/dl; peripheral smear was normal and showed no rouleaux formation; no nucleated red blood cells; and sickling test, negative. Lupus erythematosus-cell test, rheumatoid factor and antinuclear antibodies in the serum were negative, and serum venereal diseases research laboratories (VDRL) test was non-reactive. Routine blood biochemistry revealed normal values for the following: fasting sugar, urea, creatinine, cholesterol, HDL cholesterol, LDL cholesterol, VLDL, and triglycerides. Apolipoprotein fractions: Apo-A, Apo-B, Lpa were normal. Serum electrolytes, proteins, liver function tests, were also within normal limit. Anticardiolipin antibodies were elevated: IgG, 22.8 U/ml (normal values < 10 U/ml); IgM, 23.7 U/ml (normal values < 5 U/ml). The levels of IgG and IgM at a prior presentation (one year earlier with left hemiparesis) were also high (24 U/ml and 22 U/ml, respectively). Serum complements C3 and C-4, protein C, protein S and antithrombin III levels were normal. The clotting time was 4 min, partial thromboplastin time (PTT) was 13-15 s. Electrocardiography (ECG) showed T wave inversion in V4-V6. Transthoracic echocardiography was normal. Cranial computed tomography (both plain and contrast studies) showed a recent infarct in the territory of left middle cerebral artery (MCA). The patient received intravenous mannitol and furosemide. He was administered a loading dose of phenytoin sodium (20 mg per kilogram), followed by a maintenance dosage of 5 mg per kilogram body weight. He was put on elective ventilation, but did not improve and succumbed on the second day of admission. Postmortem lumbar puncture revealed blood-stained CSF, with slightly elevated glucose (68 mg/dl) and protein (70 mg/dl) and no reactivity for VDRL.

#### Pathological examination

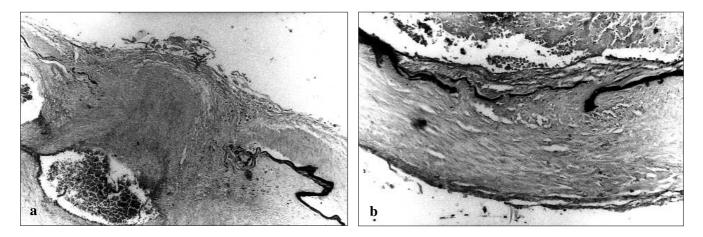
Postmortem examination of the brain was only conducted 6 h after death. The brain was fixed in formalin. After gross examination of the brain and cerebral vessels, representative blocks of tissue were processed for paraffin sectioning. In addition to routine hematoxylin-eosin preparation, appropriate staining was carried out for delineation of lesions.

On gross examination, the brain had patchy subarachnoid hemorrhage. The right half of the hemisphere was small and atrophic, while the left half was edematous and softened. The base of the brain revealed thrombosis of the left internal carotid artery, extending to the main branches of the middle cerebral and A1 segments of the anterior cerebral arteries, with resultant softening. The cerebral vessels of the opposite side were patent. There was no evidence of atherosclerosis, hypoplasia, or constriction or beading of the cerebral vessels. The crus cerebri, pons and medullary pyramid on the right half were small and atrophic. The right crus cerebri had a Kernohan's notch secondary to a left-to-right shift of the hemispheres. Serial coronal slicing of the brain further revealed atrophy of the right half of the brain and a healed cystic infarct of the right basal ganglia and thalamus extending to the sylvian fissure. On the left, an ischemic infarct with focal areas of hemorrhagic softening involving the left middle cerebral and anterior cerebral artery territories was seen. Another discrete, superficially healed infarct was seen in the right occipital lobe. Histological examinations of the representative sections through different areas of the brain revealed healed infarcts involving the right temporal and insular cortex, basal ganglia, hippocampus and the crus cerebri while the corresponding zones on the left had an acute ischemic infarct and intense congestion of vessels. The major cerebral vessels and their branches on the right side had organized and recanalized thrombi, while on the left fresh side thrombi totally occluding the lumen were seen. The media of the internal cerebral and middle cerebral arteries were disorganized bilaterally, but more on the left by islands of fibroplasia, continuous with intimal fibrosis and thickening

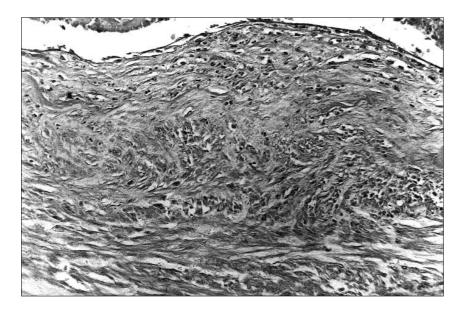
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through the disrupted internal elastic lamina (Fig. 1a). The internal elastic lamina was disorganized by fragmentation, duplication and rupture (Fig. 1b). In focal areas of smaller arterial branches, intimal cushions of fibroplasia, entrapping inflammatory cells and indicating recently organizing thrombi, were found to constrict the lumen (Fig. 2). The media was unevenly thickened by proliferating smooth muscle cells and fibroblasts. There was no evidence of vaculation of the medial smooth muscle cells nor mediolysis in any of the vessels. There was no deposition of fibrin or hemorrhages in the medio-advential junction, nor arterial wall gaps, as described in segmental mediolytic arteritis, although medial muscle coat thickness was variably reduced. The outer layer of adventitia of medium-sized branches of the MCA on both the sides had lymphoplasmacytic infiltrates. In the parenchyma with acute infarct, occasional small vessels showed extravasation of fibrin deposition on the vessel wall and platelet thrombi in the lumen. The meningeal vessels were essentially normal, but for focal intimal fibrosis, with no occluding thrombi and did not show fibromuscular dysplastic changes.

The pathological changes in the major cerebral vessels were characteristic of medial and intimal fibromuscular dysplasia associated with advential mononuclear inflammatory cell infiltration and varying stages of evolution of thrombotic phenomenon.



**Fig. 1 a** Close-up view of the fibromuscular lesion shows discontinuity of the elastica, extension of the subintimal fibrotic lesion compressing the media. Verhaff Von Geison (VVG) x 160. **b** Segment of the internal carotid artery showing disruption, thickening and duplication of the internal elastic lamina and irregular thinning of media. VVG x280



**Fig. 2** Smaller branch of right MCA showing subintimal thrombus entrapping inflammatory cells. The media is thinned. HE x280

#### Discussion

The anticardiolipin antibodies are a class of acquired immunoglobulins that bind a variety of anionic phospholipids and represent a subset of anti-endothelial autoantibodies. The association with arterial or venous occlusions is due to the thrombogenic nature of these lipoglobulins. The neurological syndromes associated with anticardiolipin antibodies include transient cerebral ischemic attacks, small stroke syndromes, arterial and venous retinal occlusive disease, cerebral arterial and venous thrombosis, migrainous headaches, Degos' disease, Sneddon's syndrome, chorea, seizures and optic neuritis. Pathological studies of cerebral arteries thrombosed in association with anticardiolipin antibodies are quite rare [2, 8]. The findings on autopsy indicate that most neurological symptoms reflect an ischemic arteriopathy in the medium-sized vessels, with bland thrombotic vasculopathy and fibrin thrombi in small vessels in the absence of inflammatory component.

Fibromuscular dysplasia (FMD) is a rare cause of stroke in the young, and more than one risk factor is usually associated with it, e.g. hypertension, dissection of the vessel, or thrombosis [9-11]. It is a vasculopathy characterized by a nonatheromatous, noninflammatory fibroplasia of the tunica media and intima, with disruption of elastica in small and medium-sized arteries [9]. Although FMD was initially described in the renal arteries [10], the cerebral vessels are involved in 25%-30% of cases. FMD of cephalic vessels is often asymptomatic and detected incidentally on angiography [9]; rarely have these been verified pathologically [6]. Our patient had cephalic arterial fibromuscular dysplasia and circulating anticardiolipin antibodies manifesting with occlusion of the carotid artery and extending peripherally. Clinically, the patient did have features of an anticardiolipin syndrome (visual loss, optic atrophy, angina, and recurrent strokes). However, so far co-existence of fibromuscular dysplasia with anticardiolipin antibody positivity has not been described in the literature, although a similar association has been recorded in renal arteries and in vessels of the lower limbs [7]. The pathogenic relationship of FMD and the presence of circulating anticardiolipin antibodies in the evolution is not clear. Two pathogenic mechanisms have been considered:

- (a) The preexisting FMD in conjuction with postischemic turbulence in blood flow causes mechanical shearing injury of the endothelial surface exposing the cryptic phospholipid sites, inducing the production of anticardiolipin autoantibodies, furthering thrombogenesis.
- (b) Interaction of anticardiolipin autoantibodies, formed by an altered immune mechanism, with the vascular endothelium may lead to release of immune mediators and growth factors. These trophic elements lead to focal disorganized proliferation of subendothelial fibroblasts and myoblasts, mechanically disrupting and splitting the elastica, thus leading to evolution of fibromuscular dysplasia.

Immune-mediated inflammation may also take part in causing vessel wall damage and dysplastic fibromuscular dysplastic nodules. The histological features in the present case are in variance to segmental mediolytic arteritis (SMA). While SMA is characterized by vacuolation of smooth muscle cells, progressing to mediolysis, arterial gaps and arterial dissection [12, 13] in FMD, fibrogenesis predominates leading to disorganized cushions, compromising the lumen and thickening of the vessel wall. Periadventitial inflammation seen in the present case may also be seen in mediolytic arteritis. Both FMD and SMA can have immune injury as the initiator factor, although the phenotypic expression appears to be distinctly different. Slavin et al. [14] suggested that segmental arterial mediolysis is a precursor to fibromuscular dysplasia. What transforms the vacuolar, mediolytic lesion to a fibromuscular dysplastic lesion is not clear, although the latter may represent an exaggerated reparative process to offset loss of medial muscle wall secondarily causing thromboembolic phenomenon. The thrombotic phenomenon observed may be a secondary event, even though clinically of great relevance. One needs yet to explain the mechanistic events in the evolution of FMD in the absence of anticardiolipin antibodies. A detailed study of similar cases with special emphasis on mechanical factors, immune events, hemorrhealogy and thrombogenesis will provide further insight into the interplay of events, clinically manifesting as "stroke in young".

Fibromuscular dysplasia associated with extensive intracranial vascular thrombosis and anticardiolipin positivity are the unique features of this case.

**Sommario** Viene riportato un caso di displasia fibromuscolare (FMD) manifestatasi con un infarto non emorragico come sintomo di presentazione. Il riscontro di anticorpi anticardiolipina suggerì una patologia immunologica. Si tratta di un uomo di 40 anni che presentò un ictus preceduto da attacchi ischemici. La tomografia computerizzata (TC) cerebrale mostrò un infarto recente non emorragico nel territorio della arteria cerebrale media (MCA) e un infarto pregresso della MCA sinistra. Positiva la ricerca degli anticorpi anticardiolipina (Acl). I reperti descritti sopra furono confermati dall'autopsia che rivelò anche un quadro di displasia fibromuscolare (FMD) delle arterie carotide interna e cerebrale media dei due lati con trombosi. Il caso suggerisce per la FMD un meccanismo immunologico precedentemente non descritto per il circolo cerebrale.

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