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Vasculitis as a Cause of First-Ever Stroke

Malgorzata Wiszniewska[1] and Julien Bogousslavsky[2]
[1]*Małgorzata Wiszniewska - Neurological Department, Specialis Hospital Piła,*
[2]*Julien Bogousslavsky - Gendier Swiss Medical Network,*
Clinique Valmont, Glion/Montreux
[1]*Poland*
[2]*Switzerland*

1. Introduction

The term "vasculitis" includes a heterogeneous group of multisystemic disorders characterized pathologically by inflammation of blood vessels [1,2,3]. Inflammation can involve some, or all, of the thickness of the vessel wall. Immune complexes are a major component of vasculitis syndromes, and cellular mechanisms play a major pathogenic role in giant cell arteritis [4-12].
Arterial lesion can lead to stenosis, occlusion, and ischemic infarction [1,13]. The diagnosis of vasculitis is difficult in most cases because of the insidious nature of the disease and the fact that various parts of the circulation can be affected without definitive signs or symptoms [1, 13-15]. More often than not, the diagnosis of vasculitis is made indirectly [1,15,16]. It is an infrequent disorder and a rare cause of stroke, even in young age groups [1,17-19]. Corticosteroid therapy is the basic and most common treatment for this disease, irrespective of the antigen involved or the type of vasculitis syndrome [1,4,5,8,20,21].
The aim of this study was to use the Lausanne Stroke Registry (LSR) to evaluate how often vasculitis is a cause of first-ever stroke, and to determine the risk factors, clinical and radiological patterns, and early outcome for stroke with vasculitis.

2. Patients and methods

2.1 Patients

The patients studied were those enrolled in the LSR [22] between January 1, 1980, and December 31, 1998. All patients were admitted to the Department of Neurology for first-ever stroke and were evaluated by at least one neurologist with stroke subspecialty training and by other specialists, depending on the accompanying symptoms (often a rheumatologist).
All patients underwent a head CT or MRI, cardiac investigation (all by ECG, and, in most instances, by transthoracic or transesophageal echocardiography, with Holter ECG when needed), and Doppler investigation of the extracranial arteries. Serological or immunological testing was carried out when infection or immunological disease was suspected. Depending on need, patients also underwent cerebrospinal fluid (CSF) analysis and cerebral arteriography (including MRI angiography), while selected patients had a tissue biopsy. Patients with toxic vasculopathies were excluded due to the lack of clear-cut criteria for the differential diagnosis of pure vasculitis and drug–induced multiple vasospasm.

2.2 Methods

Vasculitis was recognized on the basis of a comprehensive medical history and physical examination and the presence of vascular lesions in the CT or MRI with abnormalities in appropriate laboratory blood tests, and positive auto-antibodies or positive serological tests or bacteriological culture (blood and/or CSF) for infections. The criteria of the American College of Rheumatology were used to establish the correct diagnosis of vasculitis [1,4,13,16,20,23-25]. The diagnosis was confirmed by a characteristic vessel wall inflammatory reaction, with irregularities in the intracranial vessels on angiography in some cases. In all patients, other causes of stroke were first excluded.

The functional status at 1 month after stroke onset (early outcome) was measured using a 5-point scale, with 1 indicating no disability and 5 death. A good outcome was defined as patients with no or mild disability (points 1 and 2), while a bad outcome was defined as patients with moderate or severe disability, or death (points 3-5).

2.3 Statistical methods

Frequencies were compared using Fisher's exact test for dichotomous factors or the chi-squared test when more than 2 categories were present. Age differences were compared using Wilcoxon's rank-sum test.

3. Results

Between January 1, 1980 and December 31, 1998, 27 of the 4,086 (0.7 %) patients in the LSR were found to have vasculitis, 15 (55.5 %) having primary vasculitis (PV) and 12 (44.5 %) secondary vasculitis (SV). The mean age of all stroke patients with vasculitis was 54.2 years, significantly lower than that of the 4,059 patients with stroke without vasculitis (mean age 63.5 years, p= 0.02). The frequency of vasculitis in men and women was similar, being 0.76% and 0.5%, respectively (p=0.43). The 27 patients consisted of 11 men and 4 women with PV (male/female ratio 2.75; mean age, 61.3 years, range 20-81) and 8 men and 4 women with SV (male/female ratio 2.0; mean age, 45.3 years, range 22-81). Risk factors were found in 17 of the 27 patients (63%), of whom 11 had hypertension (41% vs 49% of patients without vasculitis; p=0.2) and 8 (29.6%) were active smokers. Other risk factors, which were rare, were only seen in single patients (see Tables 1 and 2). The early outcome in patients with vasculitis was similar to that in patients without vasculitis, a good outcome being seen in 55.6% of patients with vasculitis and in 59% of patients without vasculitis (p=0.7).

Tables 1 and 2 show the main characteristics of the patients with vasculitis.

We would like to present GCA.

4. Discussion

Most authors have stated that vasculitis usually manifests as headache, meningeal signs, encephalopathy, psychiatric syndromes, dementia, cranial nerve palsies, and seizures, and only rarely as stroke [1,13,14,17]. There are also generally non-specific systemic symptoms, such as fever, fatigue and weight loss [19-21,25]. In our vasculitis patients, non-specific symptoms were most common, being present in 26 out of the 27 (96.3%). Meningeal signs were present in all 8 SV patients with infection. Headache-most typical sign for PACNS and GCA occurred in 15 patients (55%), but significant psychotic syndromes only in 2 (7.4%).

Characteristic	PACNS n = 6	GCA n = 6	PAN n = 3
Age, y (mean)	20▲, 26, 43, 54, 67, 75▲ (47.5)	72°, 75°, 78°, 81°, 81°, 81° (78)	45◊, 55◊, 68° (56)
Sex	2 F, 4 M	1 F, 5 M	1 F, 2 M
Risk factors, Nº patients	2 ac smok, 1 ac smok + hCh	1 diabetes+HY, 4 HY	3 HY
Neurological disorders : Hemiparesis Aphasia Hemianopsia Cerebellar Headache Disturbances cons. Epileptic seizure Meningeal signs	 3 1 2 6 1 2 1	2 (with ataxia) 4 6 1 not	2 (1 with ataxia) 1 1 not
Ictus territory : Superficial Subcortical Brainstem/cerebellum Multiple	 4 (MCA posterior reg) 1 1 (superficial)	 3 (2 ACA super ant, 1 PCA reg) 2 1	 2 (1 hemorrhagic) 1 (deep)
Arteriography, Nº patients	5: 3-intracranial vessels irregularities 1-intracranial vessels iirregularities + 50% stenosis of SA 1-sclerotic changes in both ICA▲	5: 3-arteriosclerotic changes in VAs 2-arteriosclerotic changes in ICA	2: normal view
Outcome, disability None Mild Moderate Severe Death	 6	 1 2 2 1	 1 2
Disease onset-to-stroke Latency Coexisting symptoms	Inaugural (all patients) fever (n=3), fatige (n=3)	2 mo (n=1), 1mo (n=4), inaugural (n=1) fatigue in all, polymyalgia (n=1) claudication of jaw (n=1), weight loss (n=2), fever (n=2), amblyopia on one eye (n=1)	6 y, 3 y, 2 mo polyneuropathy in all, weight loss (n=2) fever (n=1) renal failure (n=1)
Therapy, N patients	1-Dx+Antipl, 1-Antipl , 2-P, 1-P+CY,1-P+CY+FR	1-MP followed by P, 5-P	1-P, 1-MP followed byP, 1-MP followed by P+CY

PACNS=Primary angiitis of the central nervous system, GCA=Giant cell arteritis, PAN=Polyarteritis nodosa, ac smok=active smoking, F=female, M=male, HY=hypertension, hCh=hypercholesterolemia, MCA=medial cerebral artery, ACA=anterior cerebral artery, PCA=posterior cerebral artery, VAs=vertebral arteries, SA=subclavian artery, reg=region, super ant=superior anterior, cons=conciousness, , °=disease recognized before stroke, ▲=positive meningo-brain biopsy, y=years, mo=month, MP=methylprednisolone, P=prednisone, Dx=Dexamethason, CY=cyclophosphamide, FR=fraxiparin, Antipl=antiplatelet

Table 1a. Clinical and neuroradiologic features, disease onset-to stroke latency, and current therapy for 15 patients with primary vasculitis

Laboratory investigations	Type of Primary Vasculitis		
	PACNS n = 6	GCA n = 6	PAN n = 3
ESR mm/h	<10 (n=4), 35, 40	5, 11, 15, 60, 70, 120	6, 68, 90
CRP mg/l	<10 (n=5), 73	<10 (n=4), 30, 65	<10, 205, 253
Immunological abnormalities in blood and in CSF	ANA (1/320) IgG for EBV (n=1) IgG for: HS, EBV, Va (n=2)	IgG 21.17(n:8.2-17) with rise of IgG Kappa and Lambda (n=1) ANA(1/80) +Antinucleoprotein 22 +Anti-SSB 22 (n=1)	ANCA (1/320) and positive in CSF + ANA(1/80) + IgG rise (n=1) Anticentriole Ab(1/8) + ANA positive (n=1) Immune complexes C1q 24% positive (n=1)
Tissue biopsy (n patients)	2: granulomatous inflammations in a meningo-brain biopsy (fig.1)	6: mononuclear and granulomatosus with multinucleated giant cells in TA (fig.2)	3: focal segmental necrotizing vasculitis of small and medium sized arteries in liver and kidney (n=1) vasculitis signed and ischemic neuropathy in muscle-nerve biopsy (n=2)
CSF: (n patients) Protein mg/l Cytosis cells/ml blood-CSF barrier rupture	(n = 3) 7,920, 4,260, 295 93 x 10^3, 6.3, 1 (n = 3)	(n = 2) 410, 250 46 (32-polynuclear), 1 (none)	(n = 3) 1.380, 355, 895 32, 2, 2 (n = 3)

ESR=erythrocyte sedimentation, CRP=C reactive protein, E=erythrocytes, TA=temporal artery, CSF=cerebrospinal fluid, ANCA-perinuclear antineutrophil cytoplasmic antibodies, ANA=antinuclear antibodies, Ab=antibodies, EBV=Epstein-Baar virus, Va=varicella zoster, HS=herpes simplex

Table 1b. Laboratory features for 15 primary vasculitis – associated strokes

Our analysis confirmed the results of previous studies that vasculitis is a rare cause of stroke, since, out of the 4,086 patients with first-ever stroke, only 0.7% presented signs of vasculitis that could be a cause of the stroke. The mean age of the patients with vasculitis was significantly lower than that of stroke patients without vasculitis (54.2 vs 63.5 years, p=0.02). A good early outcome was seen at a similar frequency in patients with or without vasculitis (55.6% vs 59.0%). Ischemic stroke was more frequent than hemorrhagic stroke (96.3% vs 3.7%), but the group of patients with vasculitis was too small to allow a statistical conclusion to be drawn. The most common risk factor was hypertension, which occurred at a similar frequency in patients with or without vasculitis (41% vs 49%). The largest groups were patients with PACNS or Horton's disease (GCA), with 6 cases in each group.

Table 2a. Clinical and radiologic features, disease onset-to-stroke latency, and therapy for 12 patients with secondary vasculitis associated strokes

Characteristic	SLE n=1	Behçet's Disease n=2	Sarcoidosis n=1	Syphilitic n=3	Zoster n=2
Age, y (mean)	22°	23°, 28° (25.5)	47°	41, 54, 81 (58.7)	50°, 65 (57.5)
Sex: F, M	1 F	2 M	1 M	1 F, 2 M	1 F, 1 M
Risk factors N° patients	Not available	Not available	+ ac smok	3 ac smok (at 2 HY)	2HY+ ac smok + dia
Neurological disorders : Hemiparesis Aphasia Cerebellar Headache Disturbances consciousness	+	 2 2 1	+	 2+apraxia 1+apraxia 1§	 2
Ictus territory : Superficial Subcortical Deep hemispheric Brainstem Multiple	MCA reg	 2	 internal capsule	 1 PCA 1 MCA 1 ACA	 1 1
Arteriography, N° patients	Not done	1: thrombosis in intracranial sinuses	Not done	Not done	Not done
Meningeal signs	not	not	not	yes in all	yes in both
Coexisting symptoms	Erythema + fatigue	•Uveitis+art +genital ulcer + familiar history of leukaemia •oral and genital ulcers + cervical adenopathy + fever +splenomegaly	Light respiratory failure + fatigue	dilated left pupil in one fatigue in 3	•oph zoster, glauco occlusion of central A, fever •otic zoster, surdity fever
Disease onset-to- stroke latency	1 y	3 y, 1 mo	9 y	Not known	6 weeks, inaugural
Therapy	MP followed by P	P + Cyclosporin, P + FR	P + Antipl	Pen in all and in 2 + Antipl	Zoovirax +Antipl, Zoovirax + P + Anti
Outcome disability: None Mild Moderate Severe Death	 +	 1 1	 +	 2 1	 1 1

SLE=systemic lupus erythematosus, F=female, M=male, MCA=medial cerebral artery, PCA=posteri
cerebral artery, reg=region, post=posterior, ac smok=active smoking, , diab=diabetes , tc=tuberculoma, §
recognized before stroke, mo = mouth, y=year, art=arthritis, oph=ophthalmic, MP=metylpredniso
Antipl=antiplatelet

Laboratory investigations	Type of secondary Vasculitis							
	SLE N = 1	Behcet's N = 2	Sarcoidosis N = 1	Syphilitic N = 3	Zoster N = 2	Tuberculotic N = 2	Borreliosis N = 1
ESR mm/h CRP mg/l	27 not done	13, 28 <10 (both)	21 not done	12, 16 not done	25, 28 not done	40, 8 not done	5 not done
Serological Bacterial	Not available Not available	•CMV 3 (N<1,2) •EBV + HS in IgG Not available	Va (1/160) Not available	VDRL, TPH, FTA-ABS (in all positive) Not available	Oreillons IgG (both) Not available	Tox, Va, EBV (1 case) positive culture CSF (1 case)	Anti-Borreliosis Ab: IgG, IgM Not
Immunological Abnormalities	ANA 1/2560 Anti DNA 1/8 (in blood)	Rise of β-2-microglob (3,331ng/ml in CSF and 2,828ng/ml in blood) (n=1)	Not observed	Not observed	ANA 1/640 homogenic (anti-Ssa 47, anti-RNP 25, anti-Sm 22, Sc 170) (n=1)	Not observed	Not observed
CSF Protein mg/l Cytosis cells/mm3 blood-CSF barier rupture oligoclonal bands (local synthesis)	220 1x10^3 not not	460, 300 373, 62x10^3 in one not	440 17,3 not IgG, IgM	285,545;2,280 15, 8, 30 in 3 cases IgG in one	1,590, 470 77, 20 in one IgG in one	957; 2,580 10; 1,408x10^3 in 2 cases IgG in both	5,130 560 not IgG
Tissue biopsy	not available	Necrosis and inflammatory in crotal and lymphadenitis non specific in neck (n=1)	Bronchic and lung: granulomatous inflammation and vascular hyperplasia	Not available	Not available	Not available	Not available

Table 2b. Laboratory features for the 12 secondary vasculitis-associated strokes

The most significant manifestations of PACNS are reported to be headache or disturbances of consciousness [13,26-28]. All of our patients had headache, but only one showed disturbances of consciousness. The diagnosis of PACNS was proved histologically in 2 of our patients with typical granulomatous inflammation in a meningo-brain biopsy (fig.1); only one of the two underwent arteriography, which showed no significant sclerotic changes without irregularities of the intracranial vessels. In another 4 patients, the diagnosis was confirmed arteriographically (1 besides typical arterial irregularities also showed stenosis of the subclavian artery). This suggests that vasculitis and arteriosclerotic changes can coexist, which conflicts with the opinion of Woolfenden et al [23]. Many authors consider arteriography as a standard approach for patients suspected of vasculitis involving the cerebral vessels [14,23,29]. However, Vollner et al. [28] found that angiography reveals abnormalities in less than a third of PACNS patients, and these are often nonspecific. Many authors have reported that a good outcome is seen in many patients treated with prednisolone, but some have also reported a monophasic clinical course, usually with a benign outcome and not requiring aggressive immunosuppressive therapy [28,29]. A recent study shows similar results, as the early outcome was good in all our patients, one of whom did not receive glucocorticosteroids.

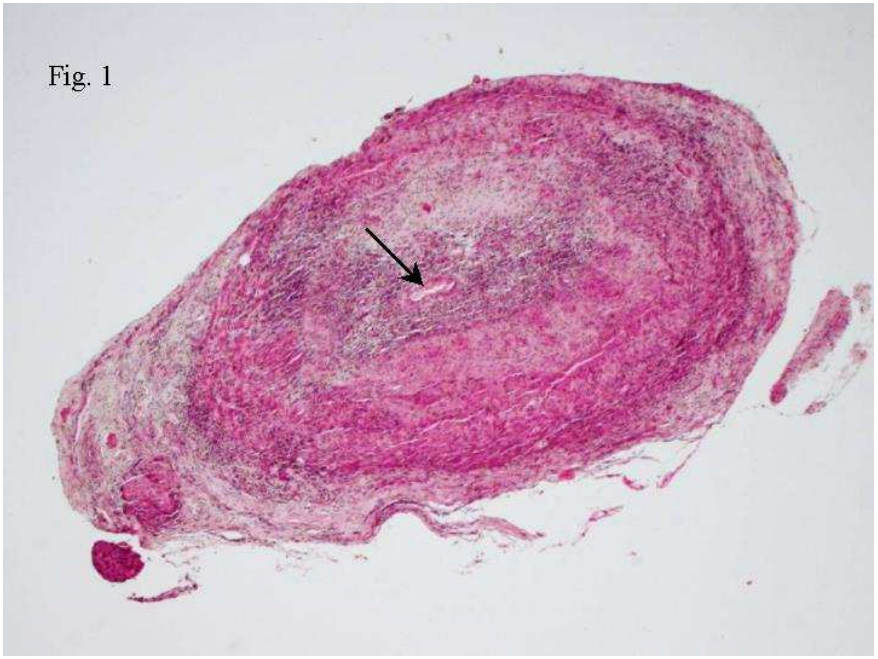

Fig. 1. PACNS – Primary angiitis of the central nervous system. Granulomatosus inflammation in meningo-brain biopsy.

In GCA, biopsy of the temporal artery is the principal means of making the diagnosis [1,2,4,12,13,30]. In all our patients, the diagnosis was confirmed histologically (fig.2). As in other reports [1,13], the outcome was good in most patients, but, in 1 patient, the early

outcome was bad, despite intensive corticotherapy similar patient describing by Staunton et al [31]. The condition of our patient deteriorated 3 days after starting therapy with prednisolone. The MRI showed a new ischemic lesion, and arteriography and Doppler investigation demonstrated occlusion of the ICA. Both Conn et al [32] and Reichart et al [19] have referred to the use of glucocorticoid therapy as a possible "double-edged sword" and suggested that progression of occlusion of the vessels may occur after control of inflammation. All strokes in PAN [20,24] occurred while the illness was controlled by glucocorticosteroid therapy.

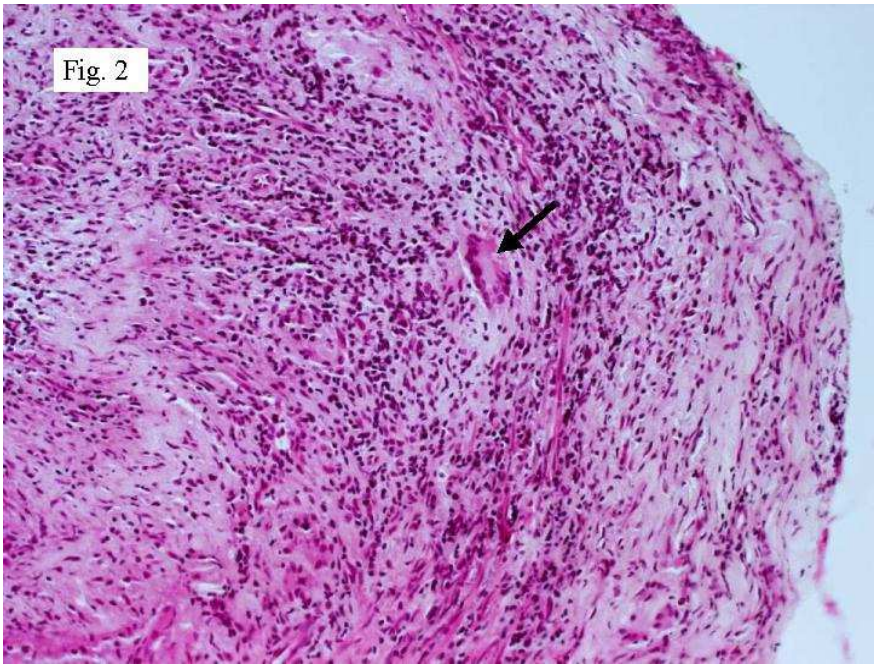

Fig. 2. GCA – Giant cell arteritis. Granulomatosus with multinucleated giant cells in the wall of temporal artery

Secondary vasculitis, which occurred in a very diverse group, was even rarer [1-4,8-10,13,33,34]. The patients with SLE, sarcoidosis, or Behçet's disease had recognized illness before the stroke and, when other causes of stroke were excluded, vasculitis was probably the cause of the cerebral ictus.

Some of our patients presented vasculitis connected with various infections. In all these patients, the history and clinical and meningeal signs was very helpful in establishing the diagnosis. The patients with lues led a style of living which could predispose to transmission of this disease, the patient with borreliosis had erythema one year previously, which was overlooked at the time, and patients with zoster vasculitis had suffered from ophthalmic and otic zoster. The diagnosis of infectious vasculitis should be based on suitable serologic or bacteriologic investigations [6,7,11,37,38]. All of these patients presented inflammatory changes in the CSF (see Table 2 b). The interval between stroke and

the beginning of disease can be variable [7,38-40]. In the 3 lues cases, it was unknown and, in 1 tuberculosis patient, stroke disclosed the disease.
To the best of our knowledge, there are no published data on a casual relationship between various types of vasculitis and first-ever stroke. The only reports we have been able to find focused on the relationship between individual types of vasculitis and stroke and case reports [5,6,10,14,19,23,25,27-31,33-40]. The results of our study indicate that various types of vasculitis can also be responsible for the first-ever brain infarction in elderly patients. In all vasculitis patients, the CT and MRI showed only non-specific brain infarcts, but, in tuberculotic vasculitis, specific signs, such as tuberculoma or hydrocephalus [11,38], were also sometimes seen. The presence of classic segmental narrowing in the cerebral angiogram suggests vasculitis [11,12,14,16,23,26] but was not seen in some cases. In agreement with published data [19,28], the presence of atherosclerotic changes did not exclude vasculitis as a cause of stroke in our patients. In GCA, the literature states that the definitive diagnostic investigation is biopsy of an affected artery [1,4,12,30], but cerebral biopsy, which can establish the diagnosis of PACNS, is not recommended in all cases [12,14-16,23].

5. Conclusions

Our observations show that vasculitis is a rare cause of stroke. Vasculitis should be suspected in patients with first –ever stroke with previously recognized systemic autoimmune disease or presenting clinical and/or biological signs of autoimmune or infectious disease. The presence of atherosclerotic changes on the arteriogram does not exclude vasculitis. Recognition of vasculitis is often indirect after exclusion of other causes of stroke, while treatment depends on the disease type. Tissue biopsy is very helpful in establishing the diagnosis. Corticosteroid therapy does not protect patients against stroke.

6. Abstract

The aims of the study were to assess how frequently vasculitis is a cause of first-ever stroke and to assess risk factors, the clinical and radiological patterns in 4,086 patients from LSR. Methods: Vasculitis was recognized using the criteria of the American College of Rheumatology. Age differences were compared using Wilcoxon's rank-sum test, frequencies - Fisher's exact or the chi-squared test. Results: Vasculitis was found in 27 (0.7%) of stroke patients. The mean age of patients with vasculitis was significantly lower than patients without vasculitis (54.2 vs 63.5 years; p=0.02). 63% patients with vasculitis had various risk factors, the most common being hypertension, with a similar frequency (41%) to that seen in patients without vasculitis (49%). A good early outcome was seen in 55.6% of the patients with vasculitis, similar to patients without vasculitis (59%; p=0.7). Conclusion: Vasculitis is a rare cause of stroke. Corticosteroid therapy does not protect patients against stroke.
Key words: Vasculitis - Angiitis – Stroke

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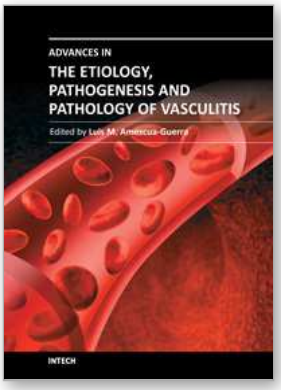

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to devote their work to this book by keeping both the text and the accompanying figures and tables lucid and memorable. Here, you will find an amalgam between evidence-based medicine to one based on eminence, through an exciting combination of original contributions, structured reviews, overviews, state-of the-art articles, and even the proposal of novel pathogenetic models of disease. The book contains contributions on the etiology and pathology of vasculitis, the potential role of endothelial cells and cytokines in vascular damage and repair as well as summaries of the latest information on several primary and secondary vasculitis syndromes. It also covers selected topics such as organ-specific vasculitic involvement and quality of life issues in vasculitis. The editor and each of the authors invite you to share this journey through one of the most exciting fields of the medicine, the world of Vasculitis.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821