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Vasculitis: Aims of Therapy/Guest Editor: R. Watts

Diagnosis and evaluation of vasculitis

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Vasculitis is inflammation of a vessel wall. The systemic vasculitides represent a highly heterogeneous group of clinicopathological entities. Vasculitis has many causes, although it produces only a few histological patterns of vascular inflammation. The clinical expression depends on the site, type and size of vessels involved. Vessels of any type in any organ can be affected, which is reflected in the wide variety of signs and symptoms. Clinically the systemic vasculitides range from benign, locoregionally restricted processes (e.g. cutaneous leucocytoclastic angiitis) to systemic vasculitis leading to life-threatening conditions [e.g. pulmonary renal syndrome in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis]. Many patients develop their disease against a background of non-specific symptoms, such as malaise, weight loss, fever and night sweats (so-called B-symptoms), which reflect constitutional symptoms. More specific symptoms derive from the type of vessels involved; this has led to the well-known classification scheme of primary systemic vasculitides (Table 1). However, in clinical practice vasculitic syndromes do not respect vessel size boundaries. In addition, discrete vasculitides with indistinguishable clinical presentations due to the predominant involvement of small vessels have a very different prognosis and require different therapies. For example, a patient with purpura caused by Henoch–Schönlein purpura has a clearly better prognosis and needs less aggressive therapy than a patient with purpura caused by microscopic polyangiitis (MPA), which is likely to progress to life-threatening organ failure if not treated by immunosuppressives. So, in addition to the clinical picture, one needs to take into account the histology and immune phenomena in the blood and tissues, and a broader differential diagnosis to avoid missing secondary vasculitides or vasculitis-like syndromes (Table 2).

Classification

In 1952, Zeek [34] became the first author to incorporate a clinicopathological assessment based on the size of the vessels involved in the inflammatory process in her classification of necrotizing vasculitis. A number of alternative classification systems were proposed later and a major break was made in the 1990s with the 1990 American College of Rheumatology criteria (ACR 1990 criteria); and the elaboration of a uniform terminology for naming, defining, classifying and diagnosing vasculitic disorders at the Chapel Hill Conference 1992 (1992 CHC definitions). The 1990 ACR criteria were reviewed in 1996 by Hunder [3]. The 1992 CHC definitions now include immunodiagnostically significant markers [e.g. ANCA in Wegener's granulomatosis (WG)] and immunohistological findings (e.g. IgA-dominant immune deposits in Henoch–Schönlein purpura) which are specific for certain diseases and were described by Jennette *et al.* [4]. The major problem with previous classification schemes was the lack of standardized diagnostic terms and definitions. As a consequence, different names had been applied to the same disease and the same name to different diseases. Therefore, the CHC committee—comprised of internists, rheumatologists, nephrologists, immunologists and pathologists who have in common extensive experience with diagnosing vasculitides—proposed the names and definitions given in Table 3.

Immunopathogenesis

Most of the vasculitic syndromes are mediated by immunopathogenic mechanisms ('immune vasculitides') and most 'immune vasculitides' are idiopathic (= 'primary' vasculitis). The immunopathogenic mechanisms of vasculitides have been classified into the four types of hypersensitivity reaction described by Coombs and Gell [35]; this classification was reviewed recently [5]. Accordingly, clinicopathological and immunohistochemical studies have led to the terms allergic angiitis (I), antibody-mediated angiitis, including the 'new' group of ANCA-associated vasculitides (II), immune complex vasculitis (III), and vasculitis associated with T-cell-mediated hypersensitivity (IV) (Table 4). Eosinophilia and elevated IgE in the blood and tissues (*in situ*) are characteristically associated with allergic angiitis and granulomatosis ('Churg–Strauss syndrome'; CSS); in 'ANCA-associated vasculitides' (AAV) few or no immune deposits are found *in situ* ('pauci-immune vasculitis'). By contrast, immune complex deposits *in situ* are the hallmark of immune complex vasculitis, which is frequently associated with low complement levels. Granulomatous arteritis is characterized by an inflammatory infiltrate induced by Th1 cells. The

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Table 1. Classification of primary systemic vasculitides

Size of dominant vessels involved	Granulomatous	Non-granulomatous
Large	Temporal arteritis Takayasu arteritis	
Medium		Classic polyarteritis nodosa Kawasaki disease
Small	WG CSS	MPA Henoch–Schönlein purpura Cutaneous leucocytoclastic vasculitis Essential cryoglobulinaemic vasculitis

Adapted from [1].

predominant immune phenomena in systemic vasculitides associated with the major hypersensitivity reaction type are given in Fig. 1.

Immunodiagnostic approach

Primary systemic vasculitides were reclassified based on ANCA serology, the presence of immune deposits *in situ*, and the size of the vessels involved. WG, MPA and CSS were subsumed in the group of ANCA-associated vasculitides, which are characterized clinically by a WG, CSS or non-granulomatous MPA inflammation commonly involving the respiratory tract and ear–nose–throat (ENT) region and by a necrotizing pauci-immune (= no or minimal immune deposits) vasculitis typically affecting small- to medium-sized vessels.

ANCA are a heterogeneous group of autoantibodies that can be subdivided by indirect immunofluorescence tests (IFTs) and by enzyme-linked immunosorbent assays (ELISAs). IFTs can distinguish two major fluorescence patterns on ethanol-fixed human granulocytes: one of these patterns, classic cANCA, is highly specific for WG, while the other, perinuclear pANCA, is commonly seen in MPA (rarely in WG), but may be detected in a wide variety of other autoimmune conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis, Felty's syndrome and chronic inflammatory bowel diseases with associated disorders).

The clinical utility of cANCA as a diagnostic marker for WG was recently confirmed in a large prospective European study undertaken with sera from vasculitis patients (sensitivity 60%, specificity 95%) [7]. However, when employed as a routine screening method for WG (defined according to ACR criteria) in patients with suspected vasculitis, the sensitivity of cANCA in a recent prospective single-centre study on 346 consecutive patients was only 28% (specificity for WG: 98%). The sensitivity rose to 83% if only biopsy-proven WG was considered [8]. A meta-analysis of 15 studies comprising 13 652 patients (including 736 cases of WG) yielded a pooled sensitivity of 66% and a specificity of 98% [9]. Taken together, these data show that the value of cANCA testing is limited by a rather low sensitivity; the greatest utility of cANCA testing may be in patients with suspected, but not yet proven, WG. This view is supported by a recent analysis of ANCA results in a large routine laboratory (Regional Immunology Laboratory, Belfast, UK). The overall positive predictive value for primary systemic vasculitides was 38% for all cANCA and only 20% for all pANCA. Specificity improved when only antinuclear antibody (ANA)-negative samples with a high ANCA titre were considered (cANCA 90%, pANCA 60%) [10]. In most, but not all cases, titres correlated with disease activity. Rising titres should alert the clinician to an increased risk of exacerbation, but are generally not regarded as an indication for intensifying therapy [11].

ELISAs are used to specify further the target antigens of ANCA, namely proteinase 3 (PR3; cANCA-positive samples have a 99% specificity for WG) [7], myeloperoxidase (MPO; 80% specificity for MPA) [7], as well as less important target antigens such as cathepsin G,

Table 2. Major categories of non-infectious vasculitis

Large vessel vasculitis
Giant cell arteritis
Takayasu arteritis
Medium-sized vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small vessel vasculitis
ANCA-associated small vessel vasculitis
MPA
WG
CSS
Drug-induced ANCA-associated vasculitis
Immune complex small vessel vasculitis
Henoch–Schönlein purpura
Cryoglobulinaemic vasculitis
Lupus vasculitis
Rheumatoid vasculitis
Sjögren's syndrome vasculitis
Hypocomplementaemic urticarial vasculitis
Behcet's disease
Goodpasture's syndrome
Serum sickness vasculitis
Drug-induced immune complex vasculitis
Infection-induced immune complex vasculitis
Paraneoplastic small vessel vasculitis
Lymphoproliferative neoplasm-induced vasculitis
Myeloproliferative neoplasm-induced vasculitis
Carcinoma-induced vasculitis
Inflammatory bowel disease vasculitis

Modified from [2].

TABLE 3. Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis[a]

Large vessel vasculitis[a]	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. *Often involves the temporal artery. Usually occurs in patients older than 50 yr and often is associated with polymyalgia rheumatica.*
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. *Usually occurs in patients younger than 50 yr.*
Medium-sized vessel vasculitis[a]	
Polyarteritis nodosa[b] (classic polyarteritis nodosa)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Kawasaki disease	Arteritis involving large-, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. *Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.*
Small vessel vasculitis[a]	
WG[c]	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels (e.g. capillaries, venules, arterioles, and arteries). *Necrotizing glomerulonephritis is common.*
CSS[c]	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and eosinophilia.
MPA[b,c] (microscopic polyarteritis)	Necrotizing vasculitis, with few or no immune deposits affecting small vessels (i.e. capillaries, venules, or arterioles). *Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*
Henoch–Schönlein purpura	Vasculitis, with IgA-dominant immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles). *Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis.*
Essential cryoglobulinaemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles), and associated with cryoglobulins in serum. *Skin and glomeruli are often involved.*
Cutaneous leucocytoclastic angiitis	Isolated cutaneous leucocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

[a]Large vessel refers to the aorta and the largest branches directed towards major body regions (e.g. to the extremities and the head and neck); medium-sized vessel refers to the main visceral arteries (e.g. renal, hepatic, coronary, and mesenteric arteries); small vessel refers to venules, capillaries, arterioles, and the intraparenchymal distal arterial radicals that connect with arterioles. Some small and large vessel vasculitides may involve medium-sized arteries, but large- and medium-sized vessel vasculitides do not involve vessels smaller than arteries. Essential components are represented by normal type; italicized type represents usual, but not essential components.

[b]Preferred term.

[c]Strongly associated with ANCA.

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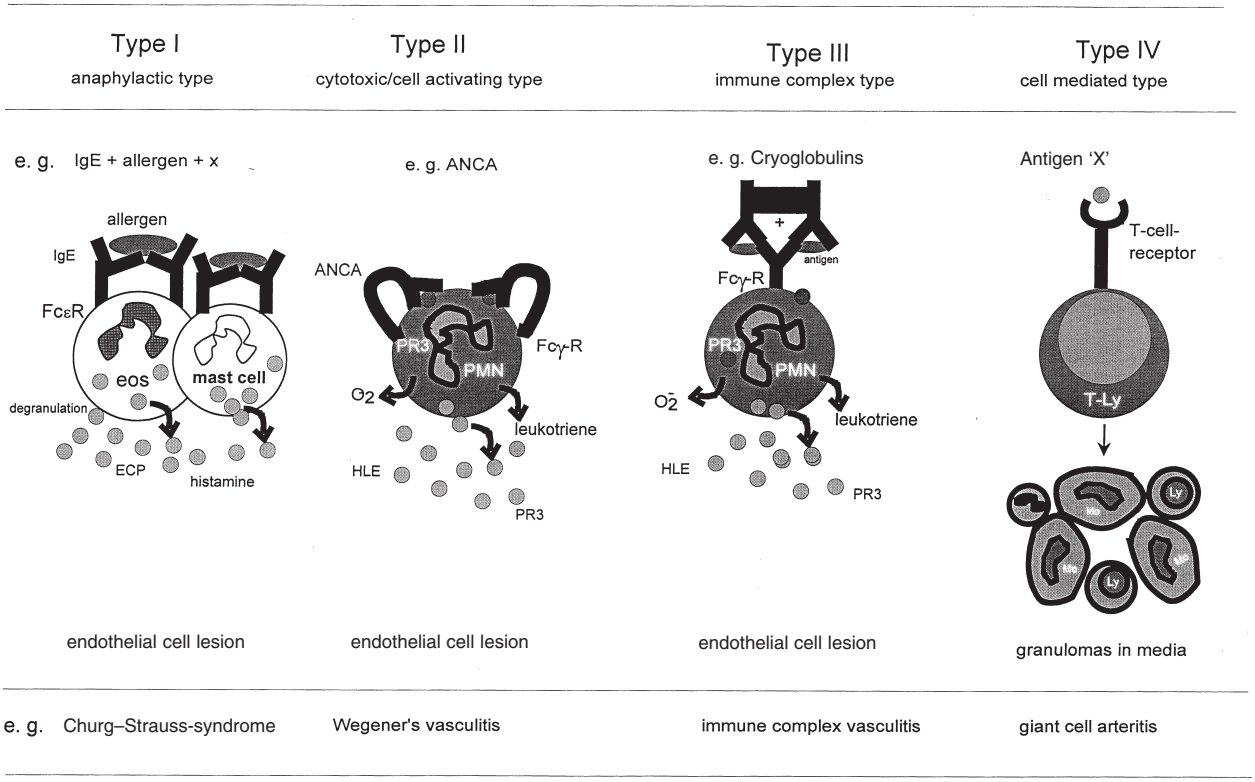

FIG. 1. Immunoallergic reactions after Coombs and Gell [35] (see [5]).

TABLE 4. Predominant immune phenomena in primarily systemic vasculitides delineate to the major hypersensitivity reaction types

Name of disease	Coombs and Gell type	Blood studies	Immunohistochemistry *in situ* (blood vessel)
CSS	I	IgE↑↑, Eos↑↑, ANCA?[a]	Pauci-immune? Eos↑↑
WG	II	PR3-ANCA	Pauci-immune[a]
MPA	II	MPO-ANCA	Pauci-immune[a]
Kawasaki disease	II	AECA	?
Polyarteritis nodosa	III	Hepatitis B virus, C′↓	Immune deposits
Henoch–Schönlein purpura	III	IgA↑	IgA-dominant immune deposits
Ess. cryoglobulinaemic vasculitis	III	Hepatitis C virus, C′↓, Cryocrit↑	IgG/mRF immune deposits
Giant cell arteritis	IV	CD3+/CD8+↓	CD3+/CD4+↑
		Activated CD68 + ↑	Activated CD68 + ↑

Type I, immediate hypersensitivity; II, antibody-mediated hypersensitivity; III, immune complex-mediated hypersensitivity; IV, T-cell-mediated hypersensitivity.

C↓, complement consumption; Eos↑↑, hypereosinophilia; CD68, macrophage marker; mRF, monoclonal rheumatoid factor; C′, complement.

[a]Pauci-immune: few or no deposits in the tissue.

Adapted from [6].

lactoferrin, lysozyme and human leucocyte elastase, which are not specific for any particular vasculitic disorder. Whether anti-bactericidal permeability increasing protein (BPI) ANCA offer further diagnostic perspectives in vasculitis is still unclear [12–14].

So, ANCA are not specific for ANCA-associated vasculitides and despite the high specificity of cANCA/PR3-ANCA for WG and of MPO-pANCA for MPA, an increasing number of 'false-positive' PR3-/MPO-ANCA have been described [11]. More recently, we and others have observed PR3-ANCA in subacute bacterial endocarditis, a condition sometimes associated with vasculitis [15]. Still, because ANCA test results are usually available before histological analyses are completed, ANCA serology remains the most important tool in the diagnostic repertoire for ANCA-associated vasculitides, especially in seriously ill patients suspected of having vasculitis. Under life-threatening conditions, therefore, therapy should be commenced based on clinical and serological findings! An overview of predominant immune phenomena in systemic vasculitides associated with the hypersensitivity reaction types (and the serological markers) is given in Table 5.

The incidence of ANCA in CSS is much lower than in WG and MPA, and their immunodiagnostic significance is limited [7]. However, active CSS is characterized by increased eosinophils in conjunction with strongly elevated IgE and eosinophil cationic protein values [17].

TABLE 5. Differential diagnostic features of small vessel vasculitides

	Henoch–Schönlein purpura	Cryoglobulin. vasculitis	MPA	WG	CSS
IgA immune deposits in vessels	+	−	−	−	−
IgG immune deposits in vessels	−	+	−	−	−
Cryoglobulins in blood and vessels	−	+	−	−	−
Hepatitis C viral genomes in blood[b] and vessels	−	HCV-RNA	−	−	−
ANCA in blood	−	−	MPO-ANCA	PR3-ANCA	(+)[a]
Missing Ig deposits ('pauci-immune')	−	−	+	+	+/−
Necrotizing granulomas	−	−	−	+[c]	+[c]
Asthma/eosinophilia (>10%)	−	−	−	−	+

[a]In about 30% of patients MPO-ANCA or PR3-ANCA were detected.
[b]Or in the cryoprecipitates.
[c]In particular in the respiratory tract.
Modified from [16].

Furthermore, endothelial cell damage in active AAV is indicated by markedly increased serum thrombomodulin (sTM) values [17]: in CSS, high levels of sTM correlate closely with the soluble interleukin-2 receptor, which has been shown to be a promising seromarker of disease activity in WG [18].

Because intermittent infections are a major differential diagnostic problem in seriously ill AAV patients (Table 6), a marker that distinguishes between the two conditions is urgently needed. Procalcitonin was recently shown to be normal in active autoimmune rheumatic disorders, but strongly elevated in concomitant bacterial infections and sepsis [19]. However, these findings have yet to be confirmed [20].

Diagnosis

A detailed patient history, physical examination and focused laboratory investigation are vital in diagnosing vasculitic disorders. The goals of the work-up include identification of a cause of the disease and/or the underlying immunopathogenetic mechanism, classification of the disease, and determination of the disease activity and extent. The latter is all the more important as stage-adapted treatment and assessment of the treatment's efficacy are only possible if there are uniform and reproducible measures of the extent and activity of organ involvement in the vasculitic disease. A prerequisite for this is a standardized evaluation of the clinical, radiological and laboratory findings by an interdisciplinary team of expert physicians (internal medicine, neurology, ophthalmology, dermatology, radiology, etc.).

Semi-quantitative scoring systems were recently developed for the standardized assessment of disease activity and extent. On the basis of the extended (ENT, lung, kidney) ELK classification [21, 22], a disease extent index (DEI) was established by our group [23]. This instrument has been well accepted by German vasculitis centres because it can be easily and quickly applied pro- and retrospectively and is valid, reliable, sensitive to change, and highly reproducible (Table 7). The DEI may also be of prognostic value in therapeutic trials. Pulse cyclophosphamide treatment, for example, proved to be less effective in patients with a DEI >7 at

TABLE 6. Summary of subacute bacterial endocarditis associated with PR3-ANCA

Wagner, 1991 [36]	GN, Osler nodes	Foc. segm. cresc. GN (IgM and C3 deposits)	*Streptococcus viridans*	nd	Recovery, ANCA neg.
Soto, 1994 [37]	Purpura, fever, weakness, haematuria, aneurysm	nd	*Streptococcus bovis*	Thickening of aortic valve	Mycotic intra-cran. cran. aneurysm. rupture
Subra, 1998 [38]	Nephrotic syndrome	Membranoproliferative GN	n.i.	Vegetations (mitral, aortic valves)	Improvement ANCA (+)
Subra, 1998 [38]	Fever, anaemia, purpura, GN	Foc. segm. cresc. GN (C1q and C3 deposits)	n.i.	Aortic vegetations	Improvement ANCA neg.
Choi, 2000 [39]	Fever, malaise, weight loss, splenomegaly	nd	*Streptococcus sanguis*	Mitral vegetations	Complete recovery ANCA neg.
Choi, 2000 [39]	Purpura, weight loss, malaise	nd	*S. viridans*	Mitral valve thickening	Complete recovery ANCA neg.

GN, glomerulonephritis; Foc. segm. cresc, focal segmental crescentic; nd, not done; *S.*, *Streptococcus*; n.i., not isolated; cran., cranial; aneurysm., aneurysmatic; neg., negative; nd, not defined.
Reviewed and modified from [39].

Table 7. The extended ELK classification led to the DEI

Organ involved	Score	Standard diagnosis procedure
ENT/upper respiratory tract	2	ENT opinion, cranial MRI, sinuscopy
Lung	2	Chest X-ray, HR-CT, bronchoscopy, bronchoalveolar lavage
Eye	2	Ophthalmology opinion, cranial MRI
Kidney	2	Urinanalysis, serum creatinine, abdominal ultrasound
Heart	2	ECG, chest X-ray, echocardiogram myocardial scintigram, coronary angiogram
Gastrointestinal tract	2	Abdominal ultrasound, endoscopy (mesenterial angiogram, laparotomy)
Skin	2	Biopsy of skin lesion
Peripheral nervous system	2	Neurology opinion, ENG, EMG (nerve biopsy)
Central nervous system	2	Neurology opinion, lumbar puncture, cranial MRI
Rheumatic complaints puncture	2	X-ray, ultrasound, diagnostic joint bone scan, serum-CK, EMG, muscular MRI, muscular biopsy
Constitutional symptoms	1	
Maximum DEI score	21 points	

Modified from [24].

the start of treatment [23]. In addition, a vasculitis activity score (Birmingham vasculitis activity score; BVAS) has been developed, validated and computerized [25]. Because of its magnitude, the BVAS is used more often in clinical studies than in daily clinical practice. Whether the two scores are complementary or could be substituted one for the other remains to be elucidated.

Laboratory tests should be used to ascertain the type of vasculitis, the organ systems affected, and the extent of organ involvement. However, many of these tests are non-specific; the erythrocyte sedimentation rate (ESR) and acute-phase proteins like C-reactive protein (CRP) only indicate that inflammation is present, but do not reveal its exact aetiology. A low complement level may be present in patients with immune complex vasculitis (e.g. cryoglobulinaemia) and the presence of cANCA (PR3-ANCA) strongly suggests a diagnosis of WG. Some differential diagnostic features of several forms of small vessel vasculitides are given in Table 5.

The definite diagnosis of systemic vasculitis, however, is dependent on the demonstration of vascular involvement by either biopsy or angiography. Biopsy specimens should be obtained only from clinically involved accessible tissue. Arteriograms are helpful in identifying and characterizing vasculitis of the medium-sized or larger arteries, e.g. in Takayasu arteritis.

Diagnostic route

The first step towards arriving at a diagnosis is to recognize what kind of vessel or vessels is predominantly involved. The second step is to find out whether other symptoms are present which seem to be unrelated to the pathological sequelae of vasculitis, i.e. to find out whether there are granulomatous lesions in the ENT region in WG or, more importantly, whether there are exogenous factors which may have triggered the vasculitic process, i.e. drugs, infections or neoplastic manifestations (Table 8). This search must be carried out very carefully with regard to the clinical investigation, starting with close examination of the patient's history and environment. Then imaging procedures have to be carried out in order to determine the disease extent. Various laboratory markers will additionally reflect or accord with the clinical impression with respect to disease activity (Table 5). A biopsy should next be taken from a site of tissue involvement in order to avoid false

Table 8. Secondary vasculitides

1. Inflammatory diseases of unknown aetiology
   - Systemic autoimmune diseases (e.g. vasculitides associated with systemic lupus erythematosus, Sjögren's syndrome, Behçet disease, and rheumatoid vasculitis)
   - Local chronic inflammatory diseases (e.g. ulcerative colitis)
   - Chronic granulomatous inflammation (Crohn's disease, sarcoidosis, etc.)
2. Infectious diseases
   - Viruses (e.g. vasculitides associated with HIV, CMV, etc.)
   - Bacteria (e.g. spirochaetales, mycobacteria, streptococci, tropheryma, whippeli, etc.)
   - Parasites (e.g. *Ascaris* etc.)
   - Fungi (e.g. *Aspergillus*)
3. Neoplasia
   - Non-Hodgkin lymphoma
   - Myeloproliferative diseases
   - Solid tumours
   - Atrial myxomas
4. Drug abuse (intoxication)
   - Opioids (cocaine, morphine, etc.)
5. Drug-induced (casuistic)
   - Antihypertensive (hydralazine)
   - Antithyroid drugs (propylthiouracil, methimazole, carbamizole)
   - Antibiotics (azithromycin, minocycline)
   - Antifibrotic (penicillamine)
   - Leukotriene receptor antagonist (zafirlukast, montelukast, pranlukast)

CMV, cytomegalovirus.

negative results, which is frequently the consequence of biopsies taken blind. After all, the question whether the disease is really one of the group known collectively as primary systemic vasculitis, or a secondary form (Table 8), or an infection-induced process, or something entirely new, must be answered. The increase in the number of cases of vasculitis due to growing awareness, better diagnostic tools, etc., has been accompanied by a parallel increase in the number of vasculitic syndromes associated with infections, immunodeficiencies, etc. Recently, granulomatous vasculitis affecting small cutaneous blood vessels and purpura due to leucocytoclastic vasculitis and associated with the herpes virus were observed [26, 27]. Moreover, a neurobrucellosis mimicking cerebral vasculitis [28] and a WG-like syndrome were identified as a case of primary immunodeficiency due to a defect of the MHC gene complex class I processing and presentation pathway [29].

First we reported a case of primary immunodeficiency due to a defect of the transporter associated with antigen presentation (TAP) genes, a heterodimeric complex which controls the expression of HLA class I molecules by delivering peptides from the cytosol into the lumen of the endoplasmic reticulum. Since childhood, the 36-yr-old female suffered from recurrent sinusitis/bronchitis. She later developed bronchiectasis and destructive nasal granulomata in conjunction with a generalized vasculitic syndrome that did not improve upon immunosuppression and antibiotics. A severe reduction of MHC class I molecules at the cell surface of the B-cell lines was observed, whereas MHC class II expression was not altered. Isoelectric focusing of metabolically labelled MHC class I molecules revealed that class I heavy chains remained unsialylated, consistent with a block of TAP-dependent translocation. These conclusions were confirmed by further experiments showing that peptide translocation was completely abolished. We also demonstrated that presentation of viral antigens through endogenous class I molecules was severely impaired. Immunoprecipitation and Western blotting of TAP1/2 complex showed that TAP2 was not detectable [29].

In our latest paper we reported five patients with the same genetic defect who displayed a remarkable homogeneity of clinical symptoms and disease course [30]. In conclusion, we described a novel granulomatous syndrome which can be erroneously classified as WG by applying international classification criteria, but which can easily be differentiated from WG by (1) analysing the level of expression of HLA class I molecules in peripheral blood mononuclear cells (PBMC) and (2) cANCA (PR3-ANCA) which will typically be absent in this disease. Our findings illustrate the general principle that an accurate genetic analysis of a defined syndrome can provide a better understanding of the aetiology and pathogenesis of a disease. Adults with otherwise unexplained destructive granulomatous lesions, frequent infections of the respiratory tract with or without bronchiectasis and leucocytoclastic skin vasculitis may suffer from a recessive defect in the HLA class I expression pathway. It is likely that expression of different HLA class I haplotypes by different patients may have an influence on the spectrum of their clinical symptoms and infections. Analysis of patients with defects in the class I presentation pathway is therefore of importance to understand the relationship between susceptibility to infectious diseases, autoimmune disorders and HLA class I haplotype in an outbred population.

In the diagnosis of a patient with suspected vasculitis there are no agreed upon criteria for the various categories of vasculitis. It is noteworthy that the ACR 1990 criteria were not designed for diagnosis. However, the proposed names and definitions for vasculitic disorders proposed in the 1992 CHC definitions [4] are being increasingly used for diagnosis. The diagnosis of vasculitis requires the knowledgeable integration of clinical, histological (immunohistological) and laboratory data. Chest and sinus radiographs by computed tomographic scans and/or nuclear magnetic resonance imaging may reveal occult respiratory tract disease [31, 32]. Confirmation that eyes, ears, nose or throat are involved often requires the expertise of an ENT and/or ophthalmology specialist [33]. In addition, nerve conduction studies can document the severity and progression (or regression) of peripheral neuropathy.

Evidence of conditions that are known to cause vasculitis has to be sought in every interview with the patient. The patient's history should be thoroughly screened for drug hypersensitivity, infection (hepatitis!), rheumatic diseases (including rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome), neoplastic disorders, and inflammatory bowel diseases.

Today's thinking about vasculitis is all too often restricted to the group of primary vasculitides. Doctors are less willing to consider those secondary, e.g. to the various conditions depicted in Table 8. This is probably the reason why in the past year many reports in leading journals have stated that infectious origins should always be considered. Despite the progress that has been made in the field of vasculitis within the past decade, this group of diseases still poses a challenge to doctors and scientists today, and will continue to do so in the future.

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