Vasculitis of small blood vessels – some riddles about IgA and about the complexity of transmigration

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Abstract: Research on leukocytoclastic vasculitis (LcV) provides insights into mechanisms of antibody-mediated immune responses as well as into the complex process of neutrophil transmigration. Clinical observations on immune complex vasculitis have revealed that adult patients with IgA containing immune complexes [Henoch–Schoenlein purpura (HSP)] have a higher rate of severe complications than children with HSP or adult patients with IgG or IgM containing immune complexes. This has direct impact on classification and management of vasculitis and warrants further studies on pathophysiology of IgA and on aberrant glycosylation of IgA1 associated with renal involvement.

In order to dissect the pathomechanisms specific for LcV, we have been comparing different mouse models of LcV with a non-vasculitic, acute inflammation (i.e. irritant contact dermatitis). We found that one characteristic constellation in the vasculitis models encompasses interference with both normal transmigration and activation of neutrophils. Toxic products released by activated neutrophils have the potential to damage endothelial cells. However, one still needs to reveal how exactly they exert such damaging effects during diapedesis *in vivo*, considering the short contacts between neutrophils and endothelial cells.

This review shows that research on LcV is embedded in an exciting context revealing special features of transmigration and antibody-mediated immune responses.

Key words: glycosylation, Henoch–Schöenlein purpura, IgA, leukocytoclastic, mouse model, transmigration, vasculitis

Introduction

Vasculitis, including small vessel vasculitis, encompasses a group of diseases which provide excitement to several people: worried excitement to patients or physicians and scientific excitement to researchers. Dealing with vasculitis means dealing with several different pathophysiological mechanisms and a fairly wide clinical spectrum. Luckily for many patients and physicians, the most frequent form, i.e. small vessel vasculitis caused by immune complexes, usually runs a favourable course, albeit it has the potential to result in major chronic illness. Anti-neutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitis, which involves a complex, autoimmune response, has a more severe and sometimes fatal course. Small vessel vasculitis with coagulopathy in bacteremia also has a serious prognosis because of the reactions associated with sepsis, but needs to be distinguished from small vessel vasculitides caused by direct infection of endothelial cells with a clinical spectrum reaching from major discomfort in African tick bite fever (1) to severe disease in Rocky Mountain spotted fever or epidemic typhus (2).

The therapies established for the serious, so-called ANCA-positive vasculitis so far are broadly immunosuppressive and thus not very specific, but they are at least based on controlled clinical studies (3,4). Treatments for immune complex-mediated, leukocytoclastic vasculitis (LcV) so far are neither specific nor strictly evidence-based (4,5). There is a thrilling hope that revelation of specific pathophysiological mechanisms will lead to the design of specific therapeutic measures in the different forms of vasculitis.

This article will focus on how unravelling pathophysiological mechanisms of vasculitis may contribute to (1) clinically useful modification of classification; and (2) appreciation of special features of IgA and of diapedesis of neutrophils.

Clinically useful classification of vasculitis cannot ignore pathophysiology

Dermatologists are somewhat privileged in the field of vasculitis, because most forms of vasculitis present with cutaneous lesions where their development is directly

accessible to the eye and the biopsy punch. In contrast, vasculitic lesions in other organs (e.g. kidneys, intestine, central nervous system) are more difficult to detect, to be followed over time and to be preserved for research.

Classification of vasculitis is needed 'to provide a standard way to […] describe groups of patients in therapeutic or epidemiologic studies' (6), but also to sharpen our understanding of the different courses of vasculitis, and to guide diagnostic and therapeutic efforts (5). Oddly, the committee of the American College of Rheumatology (ACR) (6) and members of the Chapel Hill Consensus conference (CHCC) (7) (Table 1) had not exploited the privileged experience of a dermatologist when they convened for classification of vasculitis.

IgA- versus IgG/IgM-positive immune complexes

The classifications of both the ACR and the CHCC have their undisputed merits as they established the size of the involved vessels as a primary criterion and as they included histopathological besides clinical features. However, they have remained somewhat incomplete in properly classifying or subdividing vasculitis of small vessels (LcV), which is the most common form (8–10).

For example, in immune complex-mediated vasculitis they have not differentiated LcV in adults from that in children, and while CHCC did not distinguish between the immunoglobulin classes of deposited immune complexes [IgA versus IgG/IgM (Fig. 1)], the ACR ignored this criterion completely. We and others have revealed that such distinctions are clinically and scientifically relevant, because (i) IgA-associated LcV [Henoch–Schönlein purpura] (HSP) of adult age has a higher rate of severe complications than HSP in children (11), and (ii) IgA-associated LcV (HSP) in both age groups has a significantly higher rate of systemic involvement (occurring usually within 6 months) than LcV associated with IgG or IgM containing immune complexes (12–14) (own unpublished analysis).

Vasculitis caused by IgG or IgM containing immune complexes was probably meant when the CHCC coined the term 'cutaneous leukocytoclastic angiitis' and introduced it as one entity besides HSP and cryoglobulinaemic vasculitis (7). As this term implies exclusive localization of vasculitis to the skin, it would mean that only IgA-positive vasculitis, but not IgG- or IgM-positive vasculitis, has systemic involvement such as arthralgias, glomerulonephritis or abdominal complaints (7,12). Although exclusive restriction of vasculitis to one organ has also been assumed to occur in the kidney or in the central nervous system, this assumption is worth a challenge. The reasons are: (i) the major cause for 'cutaneous leukocytoclastic angiitis' are immune complexes which circulate in the whole and not only cutaneous vasculature, (ii) the apparent absence of systemic laboratory or clinical signs (e.g. abdominal pain)

does not rule out systemic involvement, because the signs may remain undetected due to the short duration or low sensitivity of the diagnostic procedures (e.g. falsely negative haemoccult), and (iii) there are only few studies yet which have addressed this hypothesis. A retrospective study which has shown systemic involvement in few, but some patients with hypersensitivity vasculitis (14,15) used the ACR criteria and, therefore, did not include IgA as a criterion. It is probably undisputed that there is IgG-positive vasculitis with glomerulonephritis in systemic lupus erythematosus (SLE), but the CHCC and ACR have considered this as secondary vasculitis and not included it in their classification. We have seen patients without SLE, but with IgG- or IgM-positive vasculitis and with renal involvement, however, these and more cases need to be worked-up carefully in order to show that the term 'cutaneous leucocytoclastic angiitis' is too narrow and should perhaps be abandoned.

Vice versa, not all cases of IgA-positive immune complex vasculitis present with systemic symptoms (15–17), but this is probably part of the spectrum of HSP. There are autoimmune diseases and other conditions, where IgA is detected along the vessel wall, but not necessarily within immune complexes and without causing true vasculitis (17,18).

The clinical consequences are: (1) IgA has to be looked for by immunohistochemistry at least in adults (Fig. 1), (2) HSP of adult age has to be followed for at least 6 months; (3) as long as it has not been confirmed that 'cutaneous leucocytoclastic angiitis' really remains restricted to the skin, the clinician is well advised to watch for signs of systemic disease (e.g. at least perform urine analysis) in patients diagnosed with cutaneous leukocytoclastic angiitis, but not HSP (5).

Another consequence would be to integrate further pathophysiological aspects in the classification of vasculitis. We have tried to do so for small vessel vasculitis (Table 1) by modifying and supplementing the CHCC classification. A revision is currently attempted by members of European League against Rheumatism (EULAR) in cooperation with the ACR and members of the CHCC (this time with the participation of additional fields such as dermatology).

Another group of diseases with extravasation of erythrocytes is a heterogeneous group encompassing Degos disease and purpura pigmentosa progressive (capillaritis). They often present with lymphocytic infiltrates around and sometimes within the vessel walls. Only the latter would deserve the term vasculitis, so Degos disease with its eventually fatal gastrointestinal infarctions may well present a form of small vessel vasculitis. The same may apply for vasculitides with lymphocytic infiltrates sometimes observed in SLE. Yet, more accurate definitions are needed for their classification. In contrast, no primary vessel damage could be detected in the spectrum of so-called lymphocytic vascu-

Table 1. Classification of vasculitis

Vessels predominantly or exclusively involved	Vasculitis
Aorta and branching vessels	Takayasu's arteritis
	Giant cell arteritis (e.g. temporal arteritis)
Medium-sized blood vessels (medium-sized and small arteries and veins)	Polyarteritis nodosa group
	– Classic (systemic) PAN
	– Cutaneous (or single organ-restricted) PAN (without visceral involvement)
	– Kawasaki syndrome/infantile PAN
	Nodose vasculitis in panniculitis
	Erythema induratum Bazin (in association with *Mycobacterium tuberculosis*)
	Nodose vasculitis (no detection of *M. tuberculosis*)
	Erythema nodosum leprosum
Small-sized blood vessels (postcapillary venules, arterioles, rarely capillaries) (12,13,26)	Systemic ANCA-associated vasculitis [involving also medium-sized vessels such as small arteries, but mostly small vessels (49)]
	– Microscopic polyangiitis
	Renal limited form of MPA: pauci-immune glomerulonephritis1
	Mediated by or associated with ANCA against myeloperoxidase
	– Churg–Strauss syndrome
	– Wegener granulomatosis
	Associated with ANCA against proteinase 3 and granulomas
	Immune complex-associated vasculitis (most common form of LcV)
	(Immune complex-mediated damage of vessel wall as main pathogenic factor) for LcV
	– LcV with predominantly perivascular deposition of IgA-containing immune complexes [Henoch–Schönlein Purpura (HSP)]
	HSP of children (≤20 years of age)
	– Haemorrhagic oedema of childhood (≤2 years)
	– HSP of adult age (>20 years of age)
	– LcV without deposition of IgA- (rather IgG or/IgM)-containing immune complexes(hypersensitivity vasculitis, necrotizing or allergic vasculitis)
	– Cutaneous LcV (without apparent systemic involvement)
	– IgG/IgM-associated LcV with systemic involvement (not contained in CHCC)
	– Serum-sickness
	Immune complex-mediated damage of vessel wall as major, but not the only pathogenic factor
	– Cryoglobulinaemic vasculitis (intravascular gelation in the cold in addition to immune complex-mediated damage)
	– Urticarial vasculitis (factors causing urticae and/or disturbances in complement in addition to immune complex-mediated damage of vessel wall)
	– Normocomplementemic urticarial vasculitis
	– Hypocomplementemic urticarial vasculitis
	– Syndrome of hypocomplementemic urticarial vasculitis
	Complex forms of LcV (immune complexes may be present, but other major pathogenic factors come into effect) (deliberately excluded by CHCC as own entities)
	– LcV in conjunction with connective tissue disease (Sjögrens' syndrome, SLE, RA)
	– Acral LcV and vasculopathy in SLE
	– LcV in conjunction with neutrophilic dermatosis in M. Behcet
	– Erythema elevatum et diutinum
	– Granuloma faciale
	Vasculitis combined with coagulopathy (these infection-induced vasculitides are deliberately excluded by CHCC)
	Bacteremia, sepsis, pupura fulminans (Shwartzman-reaction)
	Vasculitis due to direct infection of endothelial cells (deliberately excluded by CHCC as own entities)
	E.g. infection with *Rickettsiae, Parvovirus B19*

This Classification of vasculitis follows the CHCC (7), but in addition, has subdivided small vessel vasculitis according to pathophysiological mechanisms, thus introducing the term, 'immune-complex-vasculitis' and subsumizing urticarial and cryoglobulinaemic vasculitis. The CHCC also does not contain the subgroups 'cutaneous PAN or PAN restricted to single organs' neither 'Erythema induratum Bazin' or 'nodose vasculitis'; which, however, are true vasculitides with panniculitis. The CHCC may have considered them as infection-related vasculitis. The CHCC has excluded forms of drug-induced and infection-induced vasculitis, which is probably appropriate for ANCA-associated vasculitides, but not so much for PSH or other immune-complex vasculitides, because these conditions are the major cause for immune complexes.
Currently, the European League against Rheumatism (EULAR) in cooperation with the ACR and members of the CHCC has started to revise classification of vasculitis; C.S. is one of the participants.

litides, so vasculitis may not be the direct reason for extravasation of erythrocytes in these conditions.

Harmful effects of IgA
The reasons why IgA containing immune complexes are more harmful than non-IgA containing complexes and why they are more prevalent in childhood diseases (see also IgA pemphigus) have not fully been elaborated. Yet, it is known, that IgA does not stimulate the classical, but only the alternative pathway of complement activation. This entails reduced removal of IgA-containing immune complexes via complement receptor 1 on erythrocytes to the
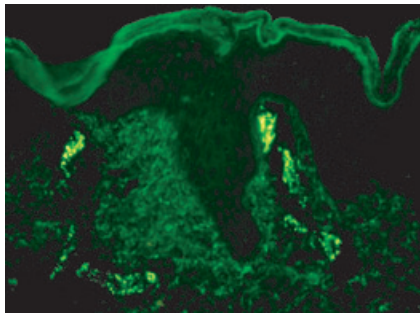
Figure 1. Perivascular deposition of IgA in a patient with Henoch–Schöenlein purpura, revealed by direct immunofluorescene (photograph kindly provided by Prof. S. Ständer, Münster).

liver. IgA1 found in the circulation and in glomerular deposits of HSP patients with nephritis is aberrantly glycosylated, similarly as in patients with IgA nephropathy (the hinge-region O-linked glycans are galactose-deficient) (19,20). Such an aberrancy exposes *N*-acetylgalactosamine-containing neo-epitopes to naturally occurring IgG or IgA1 antibodies, enabling the formation of larger immune complexes (19–22). Such complexes with abnormal O-glycosylation of IgA1 were only found in HSP patients with renal involvement, not without it (23). They were able to directly stimulate proliferation of human mesangial cells *in vitro* (21), which could be one reason for their harmful effects.

The question arises, what leads to abnormal glycosylation. IgA1 deposited in the mesangium does not appear to be the dimeric form generated in the mucosa and so it rather derives from a small population of B cells in bone marrow (24,25). However, the enzyme activity and gene expression of specific glycosyltransferases in purified B cells has recently been shown not to be reduced in patients with IgA nephropathy (25). As the pattern of O-glycosylation varies at different stages of B-cell maturation and in different immune responses, O-glycosylation profile of IgA1 is probably influenced by several mechanisms including the immunological situation in which it is produced (24). Although raised blood sugar levels do not directly induce O-glycosylation of IgA1, we screened, if there could be an indirect effect by, e.g. high blood sugar levels. An analysis of 250 patients with LcV showed that the frequency of IgA-positive vasculitides were not raised in patients with diabetes, and that the ratio between IgA- and IgG-positive vasculitides was similar in patients with raised and normal blood sugar levels (Sunderkötter et al., in preparation).

Pathophysiology: research on leukocytoclastic vasculitis helps to appreciate peculiar processes in transmigration

The undisputable classical criterion of vasculitis must be 'infiltration of the vessel wall by leucocytes', because vasculitis must be defined as an inflammation in which the vessel wall is the primary target of leucocytes (9,26). This classical histopathological criterion is easily recognized in vasculitides of medium-sized and large vessels. However, LcV involves primarily postcapillary venules. These vessels also happen to be the site of transmigration of granulocytes (27). Diapedesis is the mandatory requirement of all inflammations, so small vessel vasculitides could be the result of disturbances in transmigration (28).

To unravel its specific pathology, vasculitis needs to be distinguished from all other acute inflammations without vessel damage

Our novel methodological approach in elaborating the pathophysiological pathways of LcV was to discern the pathophysiological processes, which occur in all acute inflammations from those which occur only and exclusively in vasculitis (28). Such a distinction has not always been made as, e.g. basic processes of transmigration in 'conventional' inflammation have been unravelled by ultrastructural analysis of the Arthus reaction – a model for immune complex vasculitis (29).

In order to pursue our aim, we compared three mice models of acute vasculitides of small vessels with each other and with an acute non-vasculitic inflammation, i.e. irritant contact dermatitis. All models were established in the ear.

The immune complex-mediated Arthus reaction is elicited by generating perivascular immune complexes locally in the skin. The localized Shwartzman reaction is provoked by local cutaneous injection of LPS (lipopolysaccharide) (or IL1-ß + TNF-α) followed 24 h later by systemic application of LPS (or IL-1β + IFN-y + TNF-α). This leads to LcV only at the site of the previous local LPS injection (28). Cutaneous *Loxoscelism* is a special model induced by injection of venom from *Loxosceles reclusa*, which contains sphingomyelinase D. All these models show histologically the signs of LcV and in the Shwartzman reaction additionally, the signs of intravascular coagulation (28).

Decisively, all the vasculitic models, but not irritant contact dermatitis, involved alterations in the patterns of transmigration and concurrent neutrophil activation. The venom of *L. reclusa* is known to dysregulate and dissociate transmigration from degranulation of human neutrophils *in vitro* (30). *In vivo*, we observed neutrophils sticking next to each other on the endothelium of small vessels, almost stringed-like beads (28). This suggests that there is an arrest of granulocytes on endothelial cells prior to transmigration. For the Shwartzman reaction, we showed that it is strictly dependent on both (i) a sustained local expression of vascular adhesion molecules E-selectin and VCAM-1 for 24 h after subcutaneous LPS injection (the so-called preparatory phase), and (ii) sub-
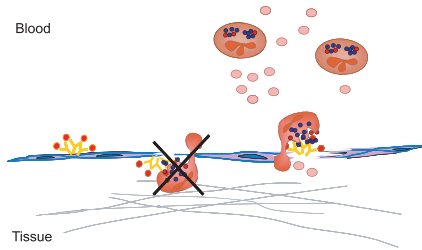
Figure 2. A simplified drawing on how one could picture the processes at the vessel wall during immune complex vasculitis: After deposition of large immune complexes at the vessel wall, neutrophils try in vain to phagocytose the firmly attached immune complexes (right half of the picture) so that their granule contents (and oxygen radicals) are released not into phagolysosomes, but into the extracellular space ('frustrated phagocytosis') which is somewhat shielded from the blood stream. The degrading enzymes released from the granules lead to local destruction of endothelial cells and extravasation of erythrocytes. According to Sindrilaru et al. (40), this process apparently takes place at the luminal site despite the blood stream, and not after neutrophils have already entered the tissue (on the left side) (drawing kindly provided by Anca Sindrilaru).

sequent activation and degranulation of neutrophils (adherent to endothelial cells) during the ensuing challenge with systemic LPS (28).

The Arthus reaction is also partially dependent on expression of E-selectin and mainly dependent on fixed deposition of large immune-complexes at the vessel wall (Fig. 2) (28). *In vitro*, granulocytes bind such large and fixed immune-complexes, but are unable to phagocytose them, so that they subsequently release their cytotoxic components into the extracellular space (degranulation and oxidative burst) (31).

Thus, the common and exclusive theme for the three models of vasculitis was alteration in activation of polymorphonuclear cells (PMN) coinciding with alterations interfering with normal diapedesis. Therefore, research on immune complex vasculitis must be research on transmigration and diapedesis of granulocytes. One cannot help but appreciate what a well-regulated and finely-tuned process transmigration must be, considering that disturbances leading to damage of the vessel wall by e.g., intimely degranulation, are rare and apparently restricted to the pathological condition termed vasculitis.

How do immune complexes lead to vessel damage?

Small circulating immune complexes are thought to be generated daily, whenever bacteria or other antigens from e.g. the oral cavity enter the blood stream during brushing of teeth or vigorous chewing and meet their specific antibodies. Large lattices of immune complexes are formed, however, when the molar concentration of antigens rises to almost equal that of antibodies (32), as occurs after intake of drugs, after infection with bacteria and virus or after exposition to large dosages of other antigens, e.g. insect

venom (33). These large immune complexes precipitate and firmly stick to the vessel wall so that they can subsequently cause degranulation and oxidative burst of neutrophils. The released degrading enzymes and oxygen radicals have been demonstrated to act synergistically in breaking down collagenous and non-collagenous components of the vascular basement membrane (34–36), and in damaging cultured endothelial cells (37). Briefly, elastase released from neutrophils can gain entry into endothelial cells, where it converts xanthine dehydrogenase into xanthine oxidase, a process finally resulting in the generation of superoxide anion (O^{2-}) and Fe^{2+}. Fe^{2+} helps to reduce H_2O_2 (which has diffused from neutrophils into the cytosol of endothelial cells) to the highly reactive oxygen radical HO^- which is likely to execute the decisive cytotoxic blow to endothelial cells (37). However, when PMN degranulate while adhering to the inner vessel wall, the released cytotoxic substances could be washed away by the blood stream whose shear stress at the vessel wall amounts to 50 dyn/cm^2 (38), or they could be partially neutralized by the high concentrations of protease inhibitors in serum (e.g. alpha 1 proteinase inhibitor, alpha 1 anti-chymotrypsin or alpha 2 macroglobulin). One could therefore hypothesize that damage to blood vessels occurs from the abluminal side, i.e. after neutrophils have already migrated through the vessel wall (Fig. 2). We tested this hypothesis with the help of CD18$^{-/-}$ mice. Their neutrophils are functionally intact, but they cannot migrate from the blood into the skin (39). When we placed them exclusively into the abluminal perivascular space by subcutaneous injection, they did not exert destructive action despite the presence of perivascular immune complexes (40). Thus, they must exert their damaging blow during diapedesis from the blood stream. The question then remains, how they manage this during their relatively short contact during transmigration. In neutrophils, adhesion to immune complexes and adhesion-induced activation appear to be closely connected to damaging vessels, because (i) respiratory burst, granule secretion and other major functions of PMN *in vitro* usually depend on stimulation both by an inflammatory stimulus and by immobilization or adherence (41–43), and (ii) *in vivo* firm adhesion of PMN to endothelial cells is required for vascular damage in the Arthus reaction (44,45). A slightly prolonged contact of neutrophils to surfaces may induce a process termed compartmentalization, which has been observed *in vitro* and encompasses shielding of proteinases by cytoplasmic protrusions of adhering neutrophils [reviewed in (46)]. This may be one explanation why products of oxidative burst and degranulation can remain highly localized to membrane regions, where FcγR binds to ligands (47).

Therefore, we suggest that in immune complex-mediated vasculitis, interactions between immune complex,

FcγR and adhesion molecules cause disturbances in transmigration and in controlled activation of neutrophils, leading to high accumulation of cytotoxic agents where FcγR binds to deposited immune complexes on endothelial cells.

These scenarios open the view on hypothetical targets for therapy. For example, in vasculitides involving immunoglobulins, blocking the signalling pathways of e.g. FcγR could present a mechanism to selectively target vasculitis-specific pathophysiology (48).

Acknowledgements

References

1 Kirschner F, Sunderkötter C, Stein A et al. Combination of different types of vasculitis in African tick bite fever. Dermatopathol Pract Concept Online 2005: **11**: online: http://dermatology.cdlib.org/

2 Sunderkötter C, Gärtner B, Essig A Infektionen der Haut. In: Marre R, Mertens T, Trautmann M, Zimmerli M, eds. Klinische Infektiologie. Jena/München: Elsevier (Urban Schwqarzenber), 2007: 633–748.

3 Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. JAMA 2007: **298**: 655–669.

4 Sunderkötter C, de Groot K. Die Therapie von Vaskulitiden und Vaskulopathien. Hautarzt 2008: **59**: 382–393.

5 Sunderkotter C, Bonsmann G, Sindrilaru A, Luger T. Management of leukocytoclastic vasculitis. J Dermatolog Treat 2005: **16**: 193–206.

6 Hunder G G, Arend W P, Bloch D A et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum 1990: **33**: 1065–1067.

7 Jennette J C, Falk R J, Andrassy K et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994: **37**: 187–192.

8 Kallenberg C G. The last classification of vasculitis. Clin Rev Allergy Immunol 2008 [Epub ahead of print].

9 Sunderkotter C, Sindrilaru A. Clinical classification of vasculitis. Eur J Dermatol 2006: **16**: 114–124.

10 Guillevin L, Dorner T. Vasculitis: mechanisms involved and clinical manifestations. Arthritis Res Ther 2007: **9** (Suppl. 2): S9.

11 Garcia-Porrua C, Calvino M C, Llorca J, Couselo J M, Gonzalez-Gay M A. Henoch-Schonlein purpura in children and adults: clinical differences in a defined population. Semin Arthritis Rheum 2002: **32**: 149–156.

12 Piette W. Primary systemic vasculitis. In: Sontheimer R D, Provost T, eds. Cutaneous Manifestations of Rheumatic Diseases. Philadelphia: Williams & Wilkins Co., 2004: 159–196.

13 Sunderkötter C, Roth J, Bonsmann G. Leukozytoklastische Vaskulitis [Leukocytoclastic vasculitis]. Hautarzt 2004: **55**: 759–785.

14 Garcia-Porrua C, Gonzalez-Gay M A. Comparative clinical and epidemiological study of hypersensitivity vasculitis versus Henoch-Schonlein purpura in adults. Semin Arthritis Rheum 1999: **28**: 404–412.

15 Garcia-Porrua C, Llorca J, Gonzalez-Louzao C, Gonzalez-Gay M A. Hypersensitivity vasculitis in adults: a benign disease usually limited to skin. Clin Exp Rheumatol 2001: **19**: 85–88.

16 Crowson A N, Mihm M C Jr, Magro C M. Cutaneous vasculitis: a review. J Cutan Pathol 2003: **30**: 161–173.

17 Magro C M, Crowson A N. A clinical and histologic study of 37 cases of immunoglobulin A-associated vasculitis. Am J Dermatopathol 1999: **21**: 234–240.

18 Crowson A N, Magro C M, Usmani A, McNutt N S. Immunoglobulin A-associated lymphocytic vasculopathy: a clinicopathologic study of eight patients. J Cutan Pathol 2002: **29**: 596–601.

19 Tomana M, Novak J, Julian B A, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. J Clin Investig 1999: **104**: 73–81.

20 Mestecky J, Tomana M, Moldoveanu Z et al. Role of aberrant glycosylation of IgA1 molecules in the pathogenesis of IgA nephropathy. Kidney Blood Press Res 2008: **31**: 29–37.

21 Novak J, Moldoveanu Z, Renfrow M B et al. IgA nephropathy and Henoch-Schoenlein purpura nephritis: aberrant glycosylation of IgA1, formation of IgA1-containing immune complexes, and activation of mesangial cells. Contrib Nephrol 2007: **157**: 134–138.

22 Lau K K, Wyatt R J, Moldoveanu Z et al. Serum levels of galactose-deficient IgA in children with IgA nephropathy and Henoch-Schonlein purpura. Pediatr Nephrol 2007: **22**: 2067–2072.

23 Allen A C, Willis F R, Beattie T J, Feehally J. Abnormal IgA glycosylation in Henoch-Schonlein purpura restricted to patients with clinical nephritis. Nephrol Dial Transplant 1998: **13**: 930–934.

24 Eijgenraam J W, van Kooten C. IgA1 glycosylation in IgA nephropathy: as sweet as it can be. Kidney Int 2008: **73**: 1106–1108.

25 Buck K S, Smith A C, Molyneux K, El-Barbary H, Feehally J, Barratt J. B-cell O-galactosyltransferase activity, and expression of O-glycosylation genes in bone marrow in IgA nephropathy. Kidney Int 2008: **73**: 1128–1136.

26 Sunderkötter C, Kolde G. Cutaneous vasculitis. In: Bos J, ed. Skin Immune System (SIS) Cutaneous Immunology and Clinical Immunodermatology. Boca Raton/New York: CRC Press, 2004: 553–563.

27 Zollner T M, Asadullah K, Schon M P. Targeting leukocyte trafficking to inflamed skin: still an attractive therapeutic approach? Exp Dermatol 2007: **16**: 1–12.

28 Sunderkotter C, Seeliger S, Schonlau F et al. Different pathways leading to cutaneous leukocytoclastic vasculitis in mice. Exp Dermatol 2001: **10**: 391–404.

29 Movat H Z, Fernando N V. Allergic inflammation. I. The earliest fine structural changes at the blood-tissue barrier during antigen–antibody interaction. Am J Pathol 1963: **42**: 41–59.

30 Patel K D, Modur V, Zimmerman G A, Prescott S M, McIntyre T M. The necrotic venom of the brown recluse spider induces dysregulated endothelial cell-dependent neutrophil activation. Differential induction of GM-CSF, IL-8, and E-selectin expression. J Clin Invest 1994: **94**: 631–642.

31 Henson P M, Oades Z G. Stimulation of human neutrophils by soluble and insoluble immunoglobulin aggregates. Secretion of granule constituents and increased oxidation of glucose. J Clin Invest 1975: **56**: 1053–1061.

32 Schifferli J A, Ng Y C, Peters D K. The role of complement and its receptor in the elimination of immune complexes. N Engl J Med 1986: **315**: 488–495.

33 Quercia O, Emiliani F, Foschi F G, Stefanini G F. Unusual reaction to hymenoptera sting: a case of Schonlein-Henoch purpura. Allergy 2007: **62**: 333–334.

34 Fligiel S E, Lee E C, McCoy J P, Johnson K J, Varani J. Protein degradation following treatment with hydrogen peroxide. Am J Pathol 1984: **115**: 418–425.

35 Fligiel S E, Ward P A, Johnson K J, Till G O. Evidence for a role of hydroxyl radical in immune-complex-induced vasculitis. Am J Pathol 1984: **115**: 375–382.

36 Weiss S J, Regiani S. Neutrophils degrade subendothelial matrices in the presence of alpha-1-proteinase inhibitor. Cooperative use of lysosomal proteinases and oxygen metabolites. J Clin Invest 1984: **73**: 1297–1303.

37 Lentsch A B, Ward P A. Regulation of inflammatory vascular damage. J Pathol 2000: **190**: 343–348.

38 von Andrian U H, Mackay C R. T-cell function and migration. Two sides of the same coin. N Engl J Med 2000: **343**: 1020–1034.

39 Mizgerd J P, Kubo H, Kutkoski G J et al. Neutrophil emigration in the skin, lungs, and peritoneum: different requirements for CD11/CD18 revealed by CD18-deficient mice. J Exp Med 1997: **186**: 1357–1364.

40 Sindrilaru A, Seeliger S, Ehrchen J et al. Site of blood vessel damage and relevance of CD18 in a murine model of immune complex-mediated vasculitis. J Invest Dermatol 2007: **127**: 447–454.

41 Lowell C A, Berton G. Integrin signal transduction in myeloid leukocytes. J Leukoc Biol 1999: **65**: 313–320.

42 Ortiz-Stern A, Rosales C. Cross-talk between Fc receptors and integrins. Immunol Lett 2003: **90**: 137–143.

43 Nathan C, Srimal S, Farber C et al. Cytokine-induced respiratory burst of human neutrophils: dependence on extracellular matrix proteins and CD11/CD18 integrins. J Cell Biol 1989: **109**: 1341–1349.

44 Stokol T, O'Donnell P, Xiao L et al. C1q governs deposition of circulating immune complexes and leukocyte Fcgamma receptors mediate subsequent neutrophil recruitment. J Exp Med 2004: **200**: 835–846.

45 Norman M U, Van De Velde N C, Timoshanko J R, Issekutz A, Hickey M J. Overlapping roles of endothelial selectins and vascular cell adhesion molecule-1 in immune complex-induced leukocyte recruitment in the cremasteric microvasculature. Am J Pathol 2003: **163**: 1491–1503.

46 Owen C A, Campbell E J. The cell biology of leukocyte-mediated proteolysis. J Leukoc Biol 1999: **65**: 137–150.

47 Naucler C, Grinstein S, Sundler R, Tapper H. Signaling to localized degranulation in neutrophils adherent to immune complexes. J Leukoc Biol 2002: **71**: 701–710.

48 Kallenberg C G. Pathogenesis of PR3-ANCA associated vasculitis. J Autoimmun 2008: **30**: 29–36.

49 Daoud M S, Gibson L E, DeRemee R A, Specks U, el-Azhary R A, Su W P. Cutaneous Wegener's granulomatosis: clinical, histopathologic, and immunopathologic features of thirty patients. J Am Acad Dermatol 1994: **31**: 605–612.