Received: 18 September 2024 | Accepted: 11 November 2024

DOI: 10.1111/ddg.15636

ORIGINAL ARTICLE

High detection rate for perivascular deposits of immunoglobulins in immune complex vasculitis from biopsies of early macular lesions

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Summary

Background: In immune complex vasculitis the detection of perivascular immunoglobulins by direct immunofluorescence (DIF) not only helps to confirm the diagnosis, but also to define the type of vasculitis (e.g., IgA-, IgG/IgM-, rheumatoid or cryoglobulinemic vasculitis). The value of DIF, though, has been questioned due to the heterogeneous yield of positive reactions in various studies. One major reason for a negative DIF is a biopsy of older lesions. To ensure selection of fresh lesions, we consistently apply morphological criteria: partially blanchable macules with only a minor petechial and papular component and in proximity to palpable or retiform purpura. This study aimed to evaluate retrospectively the detection rate attainable by this procedure.

Patients and Methods: In our department, we identified 56 patients from 2017–2024 with histologically and clinically confirmed immune complex vasculitis from whom a corresponding biopsy had been obtained.

Results: 92.9% of these patients showed perivascular deposition of at least one immunoglobulin (mostly IgA (85,7%), with or without IgG or IgM, 7,1% showed no IgA, but IgG or IgM). Biopsies positive only for C3 were considered negative. Of the IgA-positive patients 15% had a systemic, 83% a skin-limited IgA-vasculitis and 2% recurrent macular vasculitis.

Conclusions: When using defined morphological or clinical criteria for selecting appropriate biopsy sites, DIF demonstrates high sensitivity in identifying the nature of perivascular immunoglobulins in immune complex vasculitis and may serve as a valid criterion in diagnostic algorithms.

KEYWORDS
direct immunofluorescence, immune complex vasculitis, perivascular immunoglobulines, skin-limited IgA vasculitis, systemic IgA vasculitis

INTRODUCTION

When cutaneous small vessel vasculitis is suspected, detecting perivascular immunoglobulins by direct immunofluorescence (DIF) not only supports a diagnosis of immune complex (IC) vasculitis but also helps identify the specific type, such as IgA vasculitis, IgG/IgM vasculitis, cryoglobulinemic vasculitis (CV), lupus vasculitis, or rheumatoid vasculitis.[1]

Despite this relevance, the value of DIF for detection of perivascular immunoglobulins as a reliable parameter or even criterion in diagnostic algorithms is sometimes disputed,[2] due to the heterogeneous yield of positive reactions.[3] A substantial number of skin biopsies, which

have been routinely processed for investigation by DIF in order to support or specify a diagnosis of a certain IC-vasculitis have shown no deposits of immunoglobulins, even in cases in which diagnosis was otherwise unambiguously confirmed by histological and clinical criteria.[4]

Our review of respective studies or case series revealed indeed a rather wide range of positive or negative results in DIF investigations of vasculitis (Table 1). It is remarkable that most studies focused or presented data only on overall detection rates, i.e. on the sum of biopsies positive for perivascular immunoglobulins or only C3 (or even fibrinogen). However, distinguishing biopsies positive for IgA, IgG or IgM from those biopsies which are positive exclusively only for C3 without immunoglobulins is important, because only immunoglobulins, but not C3 or fibrinogen, are relevant for confirming or specifying a certain form of IC vasculitis. Detection of perivascular C3 without accompanying immunoglobulins may suggest that an IC vasculitis was present and activated complement. However, it does not identify the immunoglobulin type and therefore cannot provide insight into the specific type of IC vasculitis. Fibrinogen has no specific value in determining the type of vasculitis. In the few studies where the specific detection rate of perivascular immunoglobulins was reported or ascertainable, the rates were below 50% in two instances (47.7%[5] and 45.9%[6]) and reached 78.4% in one instance.[7] Overall percentages for DIF including C3 accordingly were usually higher, often over 80%, but with wide variations (Table 1).

The primary reason for a negative DIF result in cases of confirmed IC vasculitis, whether IgA vasculitis, cryoglobulinemic vasculitis, or another form, is likely the lesion's age and the time elapsed between lesion onset and biopsy.[8] Sequential biopsies from human patients, partially after provocation with histamine,[9,10] and animal models for IC vasculitis,[11–13] have demonstrated that positivity fades away after 72 hours. Few later studies confirmed that the disappearance of immunoglobulins begins within 48 hours, and after 72 hours, only C3 and fibrinogen remain.[8]

Yet, it is rarely possible to take this into account and to try to determine the exact age of a lesion before selecting it for a biopsy in daily hospital routine or in the setting of a dermatological outpatient clinic. Also, most dermatologists have been trained to select mature vasculitic lesions for biopsies, such as a palpable purpuric papule, in order to ensure an accurate histological analysis. Since such lesions are usually older than 72 hours, they will often not reveal perivascular immunoglobulins when they are also used for DIF.

To improve the detection rate of perivascular immunoglobulins, we use morphological criteria to select early vasculitic lesions rather than determining lesion age or duration. Specifically, we select partially blanchable macules with minor papular or petechial components as early lesions and biopsy sites for DIF, as described by Piette and Seabury Stone (1989) and Piette (1994),[14,15] since this procedure appeared to provide a higher detection rate.[16,17]

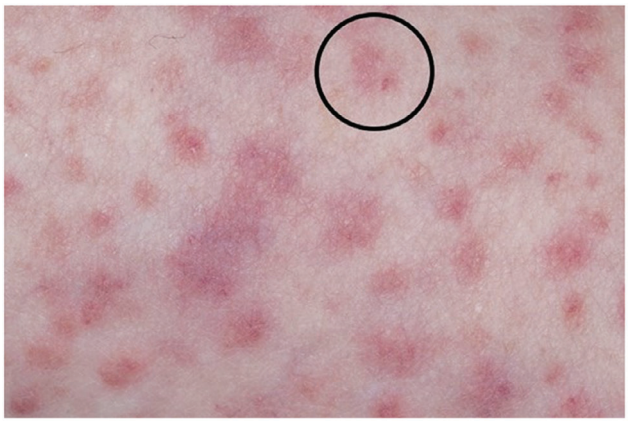

FIGURE 1 Partially blanchable macules.

This retrospective study aimed to evaluate the detection rate of perivascular immunoglobulins using this selection procedure and compare it with the immunoglobulin-positive biopsy rates reported in other studies.

MATERIALS AND METHODS

In our retrospective study we included all patients from the Department of Dermatology and Venereology, University Hospital Halle from January 2017 until August 2024 which had a histologically and clinically confirmed acute (active) IC vasculitis and from whom a skin biopsy of lesional tissue had been sent for direct immunofluorescence.

According to the standard operation procedure of our department biopsies for direct immunofluorescence were supposed to be taken from lesions with the following criteria:

- partially blanchable macules (Figure 1),
- with a minor papular or petechial component (at the most),
- in proximity to palpable or retiform purpura.

In addition, a mature vasculitic lesion, such as a purpuric papule (formalin-fixed and paraffin-embedded), was biopsied for histological analysis. Unlike early macular lesions, these lesions more reliably reveal characteristic features of leukocytoclastic vasculitis, including superficial, predominantly perivascular neutrophilic infiltrates, abundant nuclear dust (karyorrhectic debris), fibrin within the walls of postcapillary venules (fibrinoid necrosis, absent in early stages), and numerous extravasated erythrocytes.

The biopsies for DIF were frozen and sectioned at 4 µm in a cryostat. Sections were incubated with fluorescein isothiocyanate (FITC) conjugated, antisera directed against IgA, IgG, IgM and C3. A specimen was considered positive when granular deposits of one or more immunoreactants were

TABLE 1 DIF results in previous studies on vasculitis.

Study (n)	Overall positivity for perivascular deposits	Perivascular immunoglobulins	IgA	IgG	IgM	Isolated Perivascular IgG and IgM without IgA	Time of biopsy
	IgA, IgG, IgM, C3, fibrinogen	IgA, IgG, IgM					
Mackel and Jordan (1982)[7] n = 37 (with DIF)	92%	78.4%	40.5% Exclusively IgA 5.4%	8.1%	73%	IgG 0% IgM 35%	Less than 24h old
Alalwani et al. (2014)[5] n = 88 (with biopsy)	70.5%	47.7%	36.4% Exclusively IgA 21.6%	11.4%	21.6%	IgG 3.4% IgM 4.5%	Median duration from onset of rash to time of biopsy was 5.5 (20.8) months
Takatu et al. (2017)[6] n = 235 (with DIF)	70.2%	45.9%	30.64% Exclusively IgA 7.66% (IgA + C3 9.36%)	11.07%	22.13%	IgG 1.75% (IgG + C3 0.85%) IgM 2.13% (IgM + C3 10.21%)	Not specified
Barnadas et al. (2004)[23] n = 50	Not specified	Not given or ascertainable	82%	20%	56%	Not specified	Clinically recent lesion (not further defined)
Poornimambaa et al. (2017)[24] n = 34 (with DIF)	92%	Not given or ascertainable	67.6%	5.9%	17.6%	Not specified	Duration ranging from 1 to 7 days
Herrmann et al. (1980)[25] n = 57	86%	Not given or ascertainable	65%	16%	35%	Not specified	Acute vasculitis (less than 30 days, n = 26) Chronic vasculitis (longer duration, n = 23) Recurrent (n = 8)
Sais et al. (1998)[8] n = 160*	84.2%	Not given or ascertainable	64.7%	42.2%	49%	Not specified	< 24 h 24–48 h > 48–72 h > 72 h
Linskey et al. (2011)[26] n = 62	82%	Not given or ascertainable	50%	Not specified	Not specified	Not specified	Not specified
Ertekin et al. (2023)[27] n = 81	90.1%	Not given or ascertainable	43.2%	22.2%	23.5%	Not specified	Not specified (illness duration ranging from 2 to 180 days)
Gülseren et al. (2020)[3] n = 68	53%	Not given or ascertainable	42.6%	5.9%	19.1%	not specified	Median time from rash to biopsy was 14 days

(Continues)

TABLE 1 (Continued)

Study (n)	Overall positivity for perivascular deposits	Perivascular immunoglobulins	IgA	IgG	IgM	Isolated Perivascular IgG and IgM without IgA	Time of biopsy
Gower et al. (1977)[9] n = 5	80% before histamine provocation 80% after histamine provocation	Not given or ascertainable	40% before histamine provocation 40% after histamine provocation	0% before and after histamine provocation	40% before histamine provocation 80% after histamine provocation	not specified	Histamine provocation, biopsies 1 h, 4 h, 8 h, 24 h
Bouiller et al. (2016)[28] n = 99 (with DIF)	94.4%	Not given or ascertainable	40.5%	13.1%	42.9%	IgG 4.8% IgM 15.5%	Not specified
Lath et al. (2018)[29] n = 198	60%	Not given or ascertainable	35.4% Exclusively 14.1%	18.6%	24.7%	IgG 2% IgM 3.5%	Not specified (illness duration ranging from 1–2 days to over 10 years)
Sams Jr. et al. (1975)[22] n = 13	76%	Not given or ascertainable	30.8%	0%	30.8%	Not specified	Not specified
Nandeesh and Tirumalae (2013)[4] n = 198	39%	Not given or ascertainable	23%	10%	7%	Not specified	Timing of biopsy ranged from < 3 days to 6 months
Grunwald et al. (1997)[30] n = 40	92%	Not given or ascertainable	17%	28%	25%	Not specified	Not specified
Audemard-Verger et al. (2017)[20] n = 216 (with DIF)**	Not specified	Not specified	81%	Not specified	Not specified	Not specified	Not specified
Schroeter et al. (1971)[31] n = 26***	Not specified	Not given or ascertainable	0%	57.7%	44%	Not Specified	Not specified
Braverman and Yen (1975)[10] Histamine: n = 4 Clinical: n = 3****	Clinical: 100% Histamine: 100%	Clinical: 100% Histamine: 100%	Clinical: 33% Histamine: 25%	Clinical: 100% Histamine: 75%	Clinical: 100% Histamine: 75%	Clinical: 66% Histamine: 75%	Clinical: not specified Histamine: 3–4 h after injection

*Primarily so-called hypersensitivity vasculitis, but also including cryoglobulinemic vasculitis, rheumatoid vasculitis, polyarteritis nodosa, livedo vasculopathy, and Churg-Strauss vasculitis (12% in total).
**Cohort of Audemard-Verger et al. was pre-selected, because only patients who were considered to have IgA vasculitis were included. So the study likely does not exactly reflect the detection rate in an unselected group of patients with vasculitis (and detection rate was not its primary objective).
***Heterogeneous cohort, we only selected and evaluated patients with necrotizing angiitis (n = 26).
****Studied were clinical lesions and lesions after injection of histamine.

TABLE 2 Results of DIF.

Perivascular deposits	Percent	Number of patients
Any immunoglobulin	***92.9***	***52***
Overall IgA	***85.7***	***48***
Isolated IgA	69.6	39
IgA + IgM	8.9	5
IgA + IgG	1.8	1
IgA + IgG + IgM	5.4	3
Non-IgA (exclusively IgG and/or IgM)	***7.1***	***4***
IgM	3.8	2
IgG	1.8	1
IgM + IgG	1.8	1
Negative (no perivascular deposits)	***7.1***	***4***

observed in the walls of one or more vessels, primarily postcapillary venules. Biopsies positive only for C3 were classified as negative in the context of this study.

We calculated the percentage of biopsies per case with detected perivascular immunoglobulins from all cases (n = 56) subjected to DIF testing.

RESULTS

Between January 1, 2017, and August 31, 2024, a total of 56 patients with cutaneous vasculitis were identified. These patients had histologically and clinically confirmed IC vasculitis, and skin biopsies of lesional tissue were submitted for DIF.

Of these 56 patients, 52 (92.9%) showed perivascular deposition of at least one immunoglobulin (IgA, IgG, or IgM) on DIF, while 7.1% showed no deposits (Table 2). Only in some cases with positive DIF was the morphology of the biopsy site explicitly documented, i.e. as partially blanchable macule; it was not documented in the four cases lacking perivascular immunoglobulins. Two of the negative cases had been treated with glucocorticoids, as had twelve of the positive cases.

Perivascular IgA was detected in 48 of the 56 cases (85.7%). Among these, five patients also had perivascular IgM, one patient had IgG, and three patients had both IgM and IgG (Table 2). Among the IgA-positive patients, 7 had systemic IgA vasculitis, characterized by postprandial abdominal pain, signs of IgA nephritis (e.g., red cell casts or dysmorphic red cells in urine), or arthritis with swollen joints. Forty patients had skin-limited IgA vasculitis, and 1 had recurrent macular vasculitis associated with hypergammaglobulinemia (hypergammaglobulinemic purpura of Waldenström).

Of note, four patients were negative for IgA, but showed exclusively perivascular IgM (n = 1) or IgG (n = 2) or both IgG and IgM (n = 1). The patient with IgM had recurrent macular vasculitis associated with hypergammaglobulinemia. One patient with IgG had myelodysplastic syndrome and may have had a gammopathy-related IC vasculitis. Another case was not further specified, while one patient with IgG showed no signs of any other form of IC vasculitis. The latter case, therefore, met the criteria for a so-called genuine (IgA-negative) IgG/IgM vasculitis.[1,18]

Regarding potential triggers of vasculitis, 44% of cases (n = 25) reported a preceding infection, including urinary tract infections (n = 8), respiratory tract infections (n = 5), bursitis (n = 2), hepatitis E (n = 1), or flu-like symptoms (n = 9). One patient experienced a flare of inflammatory bowel disease, and three patients reported taking or possibly taking additional medications (e.g., ibuprofen as needed) within four weeks prior to the onset of vasculitis.

The retrospective analysis of the data was carried out with the approval of the local ethics committee (Medical Faculty of the Martin Luther University Halle-Wittenberg, vote No. 2019/139).

DISCUSSION

In this retrospective analysis, we observed a detection rate of over 90% for perivascular immunoglobulins in patients with IC vasculitis when biopsies were taken from morphologically fresh lesions, specifically partially blanchable macules with minor papular or petechial components, located near palpable or retiform purpura. Due to the retrospective nature of the study, we cannot confirm that all lesions were selected based on the specified criteria. However, whenever these criteria were verified through photo documentation or explicit chart descriptions, the lesions were positive for perivascular immunoglobulins.

Concurrent use of glucocorticoids did not appear to markedly impair detection of perivascular immunoglobulins as long as fresh lesions still arise despite therapy. This finding underscores that perivascular deposition of immunoglobulins is a key initiating factor in IC vasculitis.

The high prevalence of patients with skin-limited IgA vasculitis in this cohort is noteworthy but not surprising, considering that *(1)* this cohort was from a dermatology department and *(2)* most statistical data on IgA vasculitis (formerly Henoch-Schönlein purpura) come from nephrology or rheumatology departments, which primarily include patients with systemic IgA vasculitis. This has contributed to the perception of IgA vasculitis as predominantly a systemic disease. It is important to note that both systemic and skin-limited IgA vasculitis are associated with the deposition of galactose-deficient IgA1, whose detection by conventional DIF is indistinguishable from that of normal IgA.[19]

The percentage of detected perivascular deposits of immunoglobulins by DIF in our study was markedly higher than the respective percentages (between 45.9% and 78.4%) in those studies which had either directly or indirectly presented the data for exclusively perivascular deposits of immunoglobulins.[5–7] It was even higher than the overall percentage of positive DIF reported in

most other studies, which included C3- or even fibrinogen-positive but immunoglobulin-negative biopsy samples in their totals. A specific retrospective analysis of the percentage of perivascular immunoglobulin deposits across all studies was not possible with the available data (Table 1).

C3 was often the most frequently detected positive component in DIF in other studies, but it does not have the same diagnostic relevance as IgA, IgG or IgM. It is formed in course of an amplification step during the complement cascade and the number of bound molecules may therefore well exceed that of any immunoglobulin and provide a longer persistence, so that it may be the only perivascular molecule left after immunoglobulins were degraded or washed away. This may be the reason why the percentages of C3-positive DIF given in several articles were markedly higher than the actual percentage of DIFs positive specifically for immunoglobulins (e.g., 70.5% overall positivity when including perivascular C3 without IgA, IgG or IgM versus 47.7% positivity for immunoglobulins).[5]

Among the studies with data on specifically perivascular immunoglobulins only two presented percentages which were similarly high as in our cohort. In the detailed study by Audemard-Verger et al. (2017),[20] 81% of 260 patients were positive for perivascular IgA. However, this cohort of systemic IgA vasculitis was pre-selected, including only patients with histologically confirmed IgA deposits, while 44 patients were excluded due to the absence of IgA deposits. In a study by Mackel and Jordan (1982),[7] we calculated that 78.4% (n = 29) of the biopsies in a cohort of 37 patients were positive for perivascular immunoglobulins. They stated that the biopsied lesions were less than 24 hours old, reflecting a similar approach to that used in our study. Other studies which mention high percentages had *a priori* pre-selected their cohorts according to positive DIF results.[21]

The studies by Braverman and Yen (1975) and Gower et al. (1977) are pioneering works, as they investigated the deposition of immunoreactants in lesions of defined age in human IC vasculitis using histamine provocation.[9,10] They had revealed that timing of biopsy is important, because biopsy specimen taken after 48 or 72 hours may be negative in DIF, probably because immune deposits are taken up by leukocytes or degraded rapidly.[10,12,22]

Only few of the studies in Table 1 have specified if and how they selected lesions for biopsies. They report a higher yield of positive DIF when biopsies were taken within an estimated time frame of 72 hours,[4,7] but they also mention the difficulty in defining a lesion time-wise, since it would require time for continued observation of the patient or patients who are capable of correctly observing and recognizing a new lesion.

We therefore had decided to utilize the morphology of the lesion as the decisive selection criterion which encompasses a partially blanchable macule with a minor papular or petechial component (Figure 1) in proximity to palpable or retiform purpura (the latter being clinically almost pathognomonic for IC vasculitis).[14,15]

Our retrospective study demonstrates that biopsies taken according to our criteria from patients with IC vasculitis are positive on DIF and reveal the nature of perivascular immunoglobulins in nearly all cases. This approach could serve as a valid criterion in diagnostic algorithms for IC vasculitis.

ACKNOWLEDGEMENTS

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

In context of vasculitis C.S. has received honoraria for lectures and advisory boards from GSK, Vifor Pharma and Novartis. L.H. and C.M. have no conflicts of interest in context of vasculitis.

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How to cite this article: Herda L, Michl C, Sunderkötter C. High detection rate for perivascular deposits of immunoglobulins in immune complex vasculitis from biopsies of early macular lesions. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*. 2025;23:479–485. https://doi.org/10.1111/ddg.15636