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BRIEF REPORT

Antiphospholipid antibodies in adult IgA vasculitis: observational study

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Abstract

We evaluated the occurrence of antiphospholipid antibodies (aPLs) in acute adult IgA vasculitis (IgAV), and potential correlations with IgAV clinical presentation. We determined lupus anticoagulants (LAs) and IgG, IgM, and IgA isotypes of anticardiolipin antibodies (aCL), antibodies against β2-glycoprotein I (aβ2GPI) and against the phosphatidylserine-prothrombin complex (aPS/PT) in prospectively collected, histologically proven IgAV, diagnosed for the first time between January 2013 and February 2018 at our secondary/tertiary rheumatology center. During the 62 months, we determined aPLs in 125 IgAV patients (56.8% male; median (IQR) age 64.7 (48.6–78.2) years). Sixty-four (51.2%) patients had aPLs. We found LAs, aPS/PT, aβ2GPI, and aCL in 24.8%, 21.6%, 13.6%, and 11.2% of cases, respectively. With 17.6%, the IgA aPS/PT was the most common aPL subtype. aPL-positive and aPL-negative patients did not differ in the clinical presentation of acute IgAV or in the frequency of thrombotic events. aPL-positive IgAV patients had significantly higher erythrocyte sedimentation rate ($p < 0.001$), and C-reactive protein ($p < 0.001$). The subset of IgA aPS/PT-positive patients more commonly had renal involvement in acute disease (RR 2.4 (95% CI 1.6–3.7)). aPLs are commonly detected during acute IgAV episodes. Patients with aPLs have similar clinical presentation, but higher markers of inflammation at than those without them. The subset of IgAV patients with IgA aPS/PT more commonly had renal involvement.

Keywords Antiphospholipid antibodies · Henoch-Schönlein purpura · IgA vasculitis

Introduction

IgA vasculitis (IgAV; formerly known as the Henoch-Schönlein purpura) is a small vessel leucocytoclastic vasculitis characterized clinically by palpable purpura, joint, gastrointestinal (GI), and renal involvement, and histologically by a predominantly IgA deposition in the inflamed vascular walls [1]. Our current understanding of adult IgAV is limited, since it has long been considered uncommon [2]. Distinctive phenotypical patterns, beyond a severe GI and kidney involvement, were recently described in adults, warranting further evaluation [3, 4].

Antibodies directed against membrane anionic phospholipids or their associated plasma proteins, collectively known as the antiphospholipid antibodies (aPLs), are the defining pathogenic finding in patients with antiphospholipid syndrome (APS) [5]. In addition to their prothrombotic effect, aPLs have a broader range of activities. They have been shown to exert a pro-inflammatory effect, activate endothelial cells and platelets which all implies a close relationship

Rheumatology in Slovenia: Clinical practice and translational research

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between inflammation and vascular thromboses [6]. Thrombotic complications can develop in systemic vasculitides and conversely vasculitis can occur in an APS patient [7, 8].

Information on the relevance of aPLs in adult IgAV is scarce. In retrospective studies that included relatively small numbers of patients, Kawakami et al. and Kimura et al. reported on an increased prevalence of IgA aCL and IgA aPS/PT antibodies in adult IgAV, and an association between IgM aPS/PT levels and GI involvement, making them a potential marker of disease activity [9–11]. Our aim was to test these putative associations of aPLs with IgAV in a prospective manner in a well-defined group of adult IgAV patients.

Methods

Setting

This observational study was conducted between 1 January 2013 and 28 February 2018 at the Department of Rheumatology, University Medical Centre (UMC) Ljubljana, Slovenia. UMC Ljubljana provides medical care to approximately 530,000 adult residents in the Ljubljana region at the secondary level and serves approximately half of the entire Slovenian population at the tertiary level.

Patients

Adults, i.e., persons aged ≥ 18 years, with IgAV diagnosed for the first time during the observation period were included. Cases from both in- and outpatient clinics were included. The diagnosis of IgAV was established according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [1]. Only histologically proven IgAV cases were included in the study.

Diagnostic work-up

After clinical evaluation, the patients underwent an extensive laboratory work-up. Laboratory investigations were performed at presentation, before the commencement of immunosuppressive treatment. Skin or renal biopsies were evaluated using bright-field microscopy and direct immunofluorescence.

In the study, we used the definitions of generalized purpura, GI, and renal involvement as reported in detail previously [3]. In brief, purpura was considered limited when it was only present below the waist and generalized when skin lesions were present both below and above the waist. GI involvement was considered severe in cases of bloody diarrhea, ileus, or bowel perforation. Renal involvement was considered severe in patients with nephrotic syndrome or nephritic urinary sediment in the setting of acute kidney injury. Overall disease activity was assessed by the Birmingham Vasculitis Activity Score, version 3 [12]. We documented treatment of acute IgAV.

Follow-up visits with predetermined clinical and laboratory tests were scheduled at 3, 6, 12, and 24 months.

Any concurrent arterial or venous thrombotic event was recorded.

Antiphospholipid antibodies determination

Antiphospholipid antibodies (aPLs) were determined on the patient's sera samples at the time of presentation and at follow-up visits. IgG, IgM, and IgA isotypes of aCL, aβ2GPI, and aPS/PT were measured using an in-house solid-phase enzyme-linked immunosorbent assay, as described previously in detail [13–15]. For all three aPL types, a value above the 99th percentile of the healthy control population was taken as significant. Lupus anticoagulant (LA) activity was determined in those patients not receiving anticoagulant treatment at the presentation. A dilute Russell viper venom time (DRVVT) test was used and a DRVVT ratio above 1.2 was considered positive for LA.

Statistical analysis

A Mann-Whitney test was used to test for differences among subgroups of patients from our cohort for metric variables. Fisher's exact test was used in case of categorical variables. p value < 0.05 was considered significant.

Ethics committee approval

The study was approved by the Slovenian National medical ethics committee.

Results

Demographic data

During the 62-month observation period, we measured aCL, aβ2GPI, and aPS/PT antibodies in 140 patients and lupus anticoagulants in 125/140 (89.3%) cases. We limited further analyses to the 125 patients with a complete aPL panel. There were 56.8% males with a male to female ratio of 1.3 in our cohort. The median patient age (interquartile range (IQR); range) at the time of diagnosis was 64.7 (48.6–78.2; 18–90) years. The median (IQR) symptom duration was 8 (5–21) days.

Antiphospholipid antibodies, the clinical picture at baseline and treatment of IgAV

aPLs were found in 64 (51.2%) patients. As a class, we detected aCL, aβ2GPI, and aPS/PT in 11.2%, 13.6%, and 21.6% of cases, respectively. Among the patients with aPL, 46/64 (71.9%), 12/64 (18.8%), 5/64 (7.8%), and 1/64 (1.5%) had single, double, triple, and quadruple positive tests, respectively. Split by an isotype, the aPLs were positive as follows: aCL IgG 10, IgM 2, IgA 3; aβ2GPI IgG 5, IgM 4, IgA 10; aPS/PT IgG 6, IgM 5, IgA 22. Second only to LA present in 31 cases (24.8%), IgA aPS/PT was found in 22 (17.6%) cases. Clinical features of aPL-negative, aPL-positive, and IgA aPS/PT-positive cases are presented in Table 1.

aPL-positive patients had a significantly higher ESR ($p < 0.001$) and CRP ($p < 0.001$) at presentation. Additionally, IgA aPS/PT-positive patients had more commonly a renal involvement than those without this antibody ($p < 0.001$; RR 2.4 (95% CI 1.6–3.7)), and this was also more severe in IgA aPS/PT-positive group ($p = 0.002$; RR 4.1 (95% CI 1.7–10.1)). Daily proteinuria in IgA aPS/PT-positive group was significantly higher than in the group without this antibody (445 (119–1534) mg vs. 144 (68–318) mg, respectively, $p = 0.016$). Five of overall 11 patients (45.4%), who developed acute renal failure, had present IgA aPS/PT antibodies (RR 3.9 (1.3–11.6), $p = 0.015$).

Three patients suffered from a thrombotic complication during the acute phase of IgAV. Two patients developed deep vein thrombosis, one with a high titer of IgG aCL and the other without aPL. The third patient was aPL negative too and developed splenic artery and vein thrombosis with a splenic infarct, which was attributed to severe renal involvement with nephrotic syndrome.

We treated patients in line with common local practice. IgAV spontaneously remitted in 28 (22.4%) cases. Topical steroids were the only treatment in 10 (8%) of patients. Indications for systemic immunosuppressive treatment were necrotic purpura, bowel involvement of any type, or severe kidney involvement. We treated 38 (30.4%) patients with intravenous methylprednisolone pulses (MP; 125–1000 mg qd, for three consecutive days). In nine patients, MP pulses were the only treatment, while the remaining 29 patients continued with oral glucocorticoids. Oral glucocorticoids were prescribed in total of 77 patients (61.6%, median (IQR) dose of 0.4 (0.3–0.7) mg/kg of body weight). We used cyclophosphamide in 13 (10.4%), dapsone in 2 (1.6%), colchicine in 1 (0.8%), and hyperimmune gammaglobulins in 1 (1.6%) cases. None of the patients required hemodialysis. Patients with thrombotic complication received anticoagulant treatment in addition to immunosuppressive treatment. In patient with splenic artery and vein thrombosis, a splenectomy was performed.

Table 1 Clinical and laboratory characteristics of IgAV cases with and without aPL and with positive IgA aPS/PT

	Antiphospholipid Abs		IgA aPS/PT
Clinical characteristics	Not present ($N = 61$)	Present[#] ($N = 64$)	Present ($N = 22$)
M gender	35	36	12
Age (years)*	64.6 (40.4–77.3)	65.3 (51.4–79.5)	66.3 (56.5–81.6)
Prior infection	23	23	3
Past malignancy	8	6	4
General symptoms	10	11	2
Generalized purpura	32	29	12
Skin necroses	30	29	12
Joint involvement	22	22	3
GI tract involvement	21	13	4
Severe GI tract involvement	4	2	0
Renal involvement	18	26	15
Severe renal involvement	5	10	7
Thrombosis	2	1	0
IgA level (g/l)*	3.9 (2.9–5.1)	4.0 (3.3–5.2)	5.3 (4.0–7.2)
ESR (mm/h)*	25 (11–40)	41 (26–54)	49 (31–62)
CRP (mg/l)*	18 (1–32)	35 (16–68)	36 (8–68)
BVAS-3*	6 (2–12)	6 (2–12)	9 (4–14)

[#] At least one aPL antibody present (aCL, aβ2GPI, aPS/PT, or LA). *Median (IQR). *M*, male; *GI*, gastrointestinal; *Severe GI tract involvement*, bloody diarrhea or ileus or surgical intervention; *Severe renal involvement*, acute kidney injury or nephrotic syndrome; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *BVAS-3*, Birmingham Vasculitis Activity Score-3

Follow-up

Follow-up data of more than 3 months were available for 66 (52.8%) patients. The remaining 59 patients either had a follow-up in less than 3 months or were lost to follow-up. Thirty-six of 66 patients (54.5%) had aPL present at baseline. During the follow-up of a median 12.5 (6.7–19.4) months, aPLs were detected in 18 patients (27.3%). aCL, aβ2GPI, aPS/PT, and LAs were found in 10 (15.2%), 7 (10.6%), 4 (6.1%, all IgA isotype), and 6 (9.1%) of cases, respectively. Twelve patients (18.2%) had a single positive test, 4 patients (6.1%) had double positive tests, and there was 1 case of triple positivity (1.5%) and 1 case of quadruple aPL positivity. Twelve patients (18.2%) relapsed during follow-up (10 with skin lesions and 2 with skin and renal involvement). Twenty patients (30.3%) had persisting urinary abnormalities (mild in 10 cases, significant (with daily proteinuria > 0.5 g) in 10 patients). Renal function worsened during the follow-up in 3 patients (4.5%). The persistence of aPL was not associated with the persistence of urinary abnormalities (p = 0.760), nor with the progression of chronic renal failure (p = 0.563). Persistently, aPL-positive patients had numerically more frequent relapses than aPL-negative patients (50% vs. 22.2%, p = 0.073).

None of the patients were diagnosed with antiphospholipid syndrome during the follow-up. One patient without persistent aPL developed superficial thrombophlebitis during follow-up. The systemic immunosuppressive treatment did not have an influence on the aPL persistency during follow-up (p = 1.0).

Discussion

We assessed the relationship between the features of adult IgAV and four types of aPL: aCL, aβ2GPI, aPS/PT, and LA at presentation. We detected aPLs in one half of our inception IgAV cohort. This is considerably higher than 1–5.6% reported in the general population and lower than > 80% aPL of the IgA isotype reported by Kawakami et al. [9, 16]. In contrast to the latter study, where the most prevalent aPL was IgA aCL present in 73% of cases, we only found IgA aCL in 5.5% of cases.

The presence of aPL overall was not associated with any distinct clinical manifestation in our IgAV cohort. However, a significant association between the IgA aPS/PT and kidney involvement in acute IgAV was found bearing a relative risk of 2.4 (95% CI 1.6–3.7). IgA aPS/PT-positive patients also more frequently developed nephrotic syndrome and/or acute renal failure (i.e., severe renal involvement). This finding, suggestive of IgA aPS/PT involvement in the IgAV glomerulonephritis, warrants further evaluation.

Currently, it is not known whether IgAV is associated with an increased risk of thromboembolism. Three patients from our cohort suffered thrombotic complications in acute IgAV, which could be explained by both prothrombotic properties of the aPL or the inflammation on its own. Yet, in AAV, another small vessel vasculitis, a close relationship between the inflammation and thrombosis is well appreciated. Stassen et al. showed that the incidence of VTE increased from 1.8/100 person-years to 6.7/100 person-years in active AAV [6, 17]. Although our current understanding of the pathogenic mechanism of increased thrombotic risk in AAV is incomplete, neutrophil extracellular traps (NETs) formation has been suggested as a plausible mechanism. NETosis was recently reported as a pathogenic mechanism in several different systemic autoimmune diseases including AAV and the antiphospholipid syndrome. In AAV, the ANCA promote NETs release and the NETs further stimulate an autoimmune response to MPO and PR3 antigens, whereas in the antiphospholipid syndrome, aβ2GPI promotes NETosis by engaging the β2GPI protein on the surface of neutrophils [18, 19]. Thus far, there are no reports of NETs formation in IgAV, but considering the central role of neutrophils in the pathogenesis of IgAV, one might speculate that the aPL in IgAV could act as promoters of NETosis and inflammation. The circumstantial evidence of a significant correlation between elevated ESR and CRP levels and aPL positivity found in our IgAV patients also suggests that the aPL may contribute to the inflammation.

Although the follow-up data were limited to only one half of the incipient cohort, this is the first study evaluating aPLs in IgAV in the long-term manner. In the followed cohort, aPLs persisted in one half of cases. The persistence of aPLs did not associate significantly with the persistence of urinary abnormalities, or with the progression of chronic renal failure. There was a trend toward more frequent relapses in the persistently aPL-positive group than in the group without persistent aPLs. With regard to thrombotic manifestations, we registered only one thrombotic event during follow-up (a superficial thrombophlebitis in an otherwise aPL-negative patient).

We are aware of limitations of our study. The study could be improved, if we determined the LA in all the patients during the observation period. For obvious ethical reasons, only a minority of our patients had a renal biopsy; therefore, the correlation between renal histology and aPL positivity could not be examined. The limitation of follow-up data to only half of the incipient cohort is another drawback and precludes firm conclusions. However, our study has also advantages. The prospective data collection and the inclusion of only histologically proven IgAV cases from both inpatient and outpatient clinics are the major strengths of this study. Though a single-center study could be perceived as a disadvantage, the ability to perform all the serological tests in a single externally validated immunological laboratory offers the advantage of test result comparability.

Conclusions

Our study elucidates that aPLs are found in one half of adult IgAV patients at presentation and persist in a half of the cases. The IgA aPS/PT antibodies are the most commonly detected isotype in acute IgA and may be associated with renal involvement.

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Compliance with ethical standards

Disclosures None.

Ethics approval and consent to participate The informed consent for this study was not required nor obtained. The study was approved by the Slovenian National medical ethics committee.

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