Original Article

The Relationship between Direct Immunofluorescence Findings and Clinical and Laboratory Parameters in Patients with Cutaneous Small Vessel Vasculitis

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Abstract

Objective: Cutaneous small-vessel vasculitis (CSVV) is a disease characterized histologically by leukocytoclastic vasculitis (LCV) and immune-complex deposition in small vessel walls. We aimed to evaluate the type of deposited immune complexes in patients with LCV and to determine the relationship between the immune-complex types and clinical and laboratory parameters. **Materials and Methods:** Patients who had been diagnosed as LCV histopathologically between 2000 and 2018 were retrospectively evaluated. Patients' medical records and pathology databases were reviewed to determine the demographic characteristics, clinical, laboratory, and histopathological findings. Direct immune fluorescence (DIF) findings to determine the immune-complex subtypes, including immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG) or C3 deposition, were evaluated. **Results:** Sixty-eight patients were included in the study. A total of 36 (53%) patients had deposition in the perivascular or vessel walls, with at least one of IgA, IgM, IgG, or C3. IgA deposition was detected in 29 (42.6%) patients, IgM in 13 patients (19.1%), IgG in four patients (5.9%), and C3 in 31 patients (45.6%). Clinical features of the patients, including triggering factors, extracutaneous involvement, lesion localization, and skin findings, were compared with DIF findings. It was found no statistically significant difference between DIF-positive and DIF-negative groups ($P > 0.05$, for all). There was also no statistically significant difference in terms of laboratory findings between the groups ($P > 0.05$, for all). **Conclusions:** Our study showed that DIF findings did not play a role in determining the clinical findings, and they did not affect laboratory parameters in CSVV.

Keywords: Direct, fluorescent antibody technique, vasculitis

Introduction

Cutaneous small-vessel vasculitis (CSVV) is a vasculitic process that involves primarily the dermal postcapillary venules and is characterized histologically by leukocytoclastic vasculitis (LCV). Although CSVV with LCV can be seen in the setting of mixed (small- and medium-sized vessel) vasculitides, the term CSVV is generally reserved for small-vessel vasculitis of the skin without medium-sized vessel involvement, irrespective of the clinical severity of the skin disease or the underlying etiology.[1] CSVV is often idiopathic in nature but maybe secondary to an underlying cause such as drugs, infections, malignancies, and systemic inflammatory diseases have been implicated in the etiology.[2]

Clinically, the typical finding is palpable purpura, which is located on the lower extremities, but also, different types of lesions may be seen in different localizations such as upper extremity and trunk. CSVV mainly affects the skin, but the renal, musculoskeletal, and gastrointestinal system (GIS) may also be involved. Patients with no systemic findings at the time of diagnosis are less likely to develop extracutaneous involvement during the disease.[2]

The primary process in the pathogenesis of CSVV is the immune complex deposition in small vessel walls. This

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is associated with the activation of complement cascade and production of C5a, which is a neutrophil polymorph chemoattractant. After polymorph influx, lysosomal enzymes are released, and this leads to blood vessel wall damage, fibrin deposition, and the release of red blood cells (purpura) into the perivenular connective tissue. There are convincing findings about the immune-complex mediated pathogenesis of the disease, one of which is that the immune complexes can usually be detected between the basal membranes of endothelial cells and the pericytes of postcapillary venules.[3]

In the literature, there are conflicting reports about the most common immune complex type in LCV and its relationship with clinical and laboratory parameters. In this study, it was aimed to evaluate the presence of immune complex deposition and its subtype, clinical, and laboratory findings in patients with CSVV and to determine whether immune complex deposition detected by direct immune fluorescence (DIF) examination is a risk factor for the development of extracutaneous involvement.

Materials and Methods

Patients

Patients who were examined with the diagnosis of CSVV between January 1, 2000, and February 28, 2018, in the Department of Dermatology were included in the study. The database of the pathology department using the term "LCV" and "DIF"were retrospectively searched. All cases of LCV with DIF findings were reviewed by a dermatologist. Other types of vasculitis or patients diagnosed only with clinical findings were excluded. Patients' medical records were analyzed by another dermatologist to determine their demographic characteristics, clinical, laboratory, and histopathological findings. The patients' medical data such as the age at the time of diagnosis, gender, triggering factors, extracutaneous involvement, lesion localization, skin findings, laboratory parameters, and DIF findings were noted on the standardized paper forms. For extracutaneous involvement, symptoms related to joint, GIS, and kidney were reviewed from the patient's medical history or clinical follow-up records. Laboratory parameters to determine extracutaneous involvement, triggering factors, or underlying causes were reviewed. Joint involvement was defined as the presence of arthritis or arthralgias in medical history or examination. Abdominal pain, melena, hematochezia, or the presence of occult blood in the stool was described as GIS involvement. Renal involvement was defined as the presence of elevated blood creatinine levels, hematuria, spot or 24-h urinary proteinuria, or renal biopsy findings. Laboratory parameters include white blood cell (WBC), hemoglobin, blood urea nitrogen, creatinine, transaminase levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antistreptolysin-O, Complement 3 (C3) and Complement 4 (C4), rheumatoid factor (RF), antinuclear antibody (ANA), extractable nuclear antibody, perinuclear antineutrophilic cytoplasmic antibody (ANCA), cytoplasmic ANCA, urinalysis, occult blood stool (OBS), and 24-h urine protein values were recorded. Immune complexes examined on DIF included immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), and C3.

This study was approved by the Ethics Committee of the university and is registered under the following number GO 18/336-02.

Statistical analyses

Statistical analyses were performed with the Statistical Package for the Social Sciences, software version 22.0. (SPSS Inc., Chicago, IL, USA). Numerical variables were summarized as mean ± standard deviation or median (minimum–maximum). Categorical variables were given as frequencies and percentages. Categorical variables were compared by Chi-square test or Fisher's exact test. A value of $P < 0.05$ was considered statistically significant.

Results

The study included 68 CSVV patients (27 males and

Table 1: Clinical characteristics of the leukocytoclastic vasculitis patients in direct immune fluorescence positive and direct immune fluorescence negative groups

Characteristics	DIF positive ($n=36$) (%)	DIF negative ($n=32$) (%)	P*
Triggering factors			
Drug	47	50	1.00
Infection	42	41	1.00
Vaccine	0	3	N/A
Bypass surgery	3	0	N/A
Extracutaneous involvement			
Renal	53	50	1.00
Joint	64	50	0.363
GI	39	16	0.062
Neurological	3	0	N/A
Scrotal	3	0	N/A
Pulmoner	3	0	N/A
Eye	3	0	N/A
Lesion localization			
Lower extremity	97	100	N/A
Upper extremity	42	44	1.00
Glutea	39	47	0.675
Trunk	33	34	1.00
Face	6	9	0.660
Skin finding			
Macule	44	25	0.155
Papule	36	38	1.00
Plaque	19	13	0.655
Patch	39	22	0.210
Petechia	11	25	0.238
Purpura	33	53	0.161
Echymoses	3	6	0.598
Bullae	17	9	0.484
Necrosis	6	13	0.410

*Chi-square test or Fisher's exact test. N/A: Not applicable, GI: Gastrointestinal, DIF: Direct immune fluorescence

41 females) with a mean age of 34.7 ± 21.9 years (range: 2–70 years). The median time from the appearance of the rash to the time of biopsy was 14 days (range: 1–3650 days).

A total of 36 (53%) patients had deposition in the perivascular area and/or on vessel walls, with at least one of IgA, IgM, IgG, or C3. The relationship between the clinical features of the patients and DIF findings were analyzed and presented in Table 1. The differences in the triggering factors, extracutaneous involvement, lesion localization, and skin findings between DIF-positive and DIF-negative groups were not statistically significant ($P > 0.05$, for all). DIF positive group was evaluated in detail according to the deposited immune-complex subtypes and summarized in Table 2. IgA deposition was detected in 29 (42.6%) patients, IgM in 13 patients (19.1%), IgG in 4 patients (5.9%), and C3 in 31 patients (45.6%). There was no statistically significant difference between IgA, IgM, IgG, and C3 positive and negative groups in terms of triggering factors, extracutaneous involvement, lesion localization, and skin findings (all, $P > 0.05$). Laboratory findings of patients were compared, and no significant differences were found between DIF positive and DIF negative groups, as shown in Table 3. There was also no statistically significant difference in terms of laboratory findings with respect to the subtypes of the immune complexes, as shown in Table 4 (all, $P > 0.05$). Due to inadequate number in the IgG group, it was not evaluated statistically.

Discussion

Multiple factors have been reported in the etiology of CSVV, but approximately 40% of cases are idiopathic.[4] In the literature, 15%–20% of cases have been associated with infections and 10%–15% with drugs. In our study, no underlying cause was found in 41% of cases.[5] The history of the drug was determined by 49% and infection in 41%. Since some patients had taken a newly started drug during the infection, both the drug and infection were defined as triggering factors in the patient. Therefore, the prevalence of drugs and infection in our study might be higher than in the literature.

Table 2: Comparison of clinical characteristics according to immune complex subtypes in direct immune fluorescence positive group

Characteristics	IgA			IgM			C3		
	Positive (*n*=29) (%)	Negative (*n*=39) (%)	*P**	Positive (*n*=13) (%)	Negative (*n*=55) (%)	*P**	Positive (*n*=31) (%)	Negative (*n*=37) (%)	*P**
Triggering factors									
Drug	48	49	1.00	62	46	0.462	45	51	0.791
Infection	45	39	0.781	62	36	0.179	36	46	0.532
Vaccine	0	3	N/A	0	2	N/A	0	3	N/A
Bypass surgery	3	0	N/A	8	0	N/A	3	0	0.532
Extracutaneous involvement									
Renal	55	49	0.778	54	51	1.00	48	54	0.824
Joint	69	49	0.155	77	53	0.202	58	57	1.00
GI	38	21	0.190	46	24	0.166	36	22	0.319
Neurological	3	0	N/A	0	2	N/A	3	0	N/A
Scrotal	0	3	N/A	0	2	N/A	3	0	N/A
Pulmoner	0	3	N/A	8	0	N/A	3	0	N/A
Eye	0	3	N/A	8	0	N/A	3	0	N/A
Lesion localization									
Lower extremity	97	100	N/A	100	100	N/A	97	100	N/A
Upper extremity	35	49	0.354	46	42	1.00	39	46	0.723
Glutea	48	39	0.575	54	40	0.551	39	46	0.723
Trunk	38	31	0.720	54	29	0.111	36	32	0.994
Face	7	8	1.00	15	6	0.241	3	11	0.366
Skin finding									
Macule	52	9	0.029	46	33	0.520	48	24	0.070
Papule	31	41	0.555	39	36	1.00	36	38	1.00
Plaque	14	18	0.747	23	15	0.428	16	16	1.00
Patch	38	26	0.412	31	31	1.00	39	24	0.310
Petechia	14	21	0.691	15	18	1.00	10	24	0.208
Purpura	31	51	0.155	31	46	0.515	32	51	0.180
Ecchymoses	3	5	1.00	8	4	0.477	3	5	1.00
Bullae	21	8	0.156	31	9	0.060	10	16	0.494
Necrosis	7	10	1.00	15	7	0.322	3	14	0.209

*Chi-square test or Fisher's exact test. N/A: Not applicable, GI: Gastrointestinal

Table 3: Laboratory findings of the leukocytoclastic vasculitis patients in direct immune fluorescence positive and direct immune fluorescence negative groups

Parameter	DIF positive (%)	DIF negative (%)	*P**
Anemia	36	34	1.00
High WBC	28	38	0.297
High ESR	53	45	0.698
High CRP	69	70	1.00
High ASO	36	33	1.00
High creatinine	14	7	0.485
High transaminases	23	23	1.00
Low C3	10	4	0.494
Low C4	24	19	0.227
RF positivity	25	11	0.621
ANA positivity	38	40	1.00
Anti-dsDNA positivity	0	0	N/A
ANCA positivity	8	0	0.501
ENA positivity	0	0	N/A
HBV positivity	4	0	1.00
HCV positivity	0	0	N/A
Proteinuria	51	60	0.658
Hematuria	31	39	0.626
OBS	30	35	0.951

*Chi-square test or Fisher's exact test. N/A: Not applicable, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, ASO: Antistreptolysin O, C3: Complement 3, C4: Complement 4, RF: Rheumatoid factor, ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded DNA, ANCA: Anti-neutrophil cytoplasmic antibody, ENA: Extractable nuclear antigen, HBV: Hepatitis B virus, HCV: Hepatitis C virus, OBS: Ocult blood stool, DIF: Direct immune fluorescence

As extracutaneous involvement, 57% of the patients had joint involvement, followed by renal involvement with 52% and GIS involvement with 28%. In the literature, it has been reported that systemic symptoms may develop in 5%–25% of the patients with CSVV, joint involvement in 15%–65% of the patients as being most commonly, genitourinary in 3%–7% and GIS involvement in 3%–5% of the patients.[6] The prevalence of joint involvement in our study was consistent with the literature, but renal and GIS involvements were found to be higher than in the literature. Patients with Henoch-Schönlein purpura (HSP) were also included in our study. It is known that the prevalence of genitourinary involvement in patients with HSP is as high as 40%–50%, and GIS involvement may be seen in 35%–65% of the patients.[7] We think that the high prevalence rates of renal and GIS involvements might be related to the inclusion of patients with HSP in our study. Nearly all of our patients (99%) had lesions on the lower extremities, which are classical localization sites for CSVV.[7] Face, which is an unusual localization site, was also affected in 7% of the patients. Purpura was the most common skin finding with 43% of the patients and this was consistent with usual lesion type in CSVV. In patients with CSVV, mild-to-moderate inflammation may be observed. WBC, ESR, and CR*P* values may be increased, but there is a greater increase in inflammation markers in case of systemic involvement. In our study, 32% of the patients had an elevation in WBC, 47% in ESR, and 63% in CRP levels, and these results support the systemic inflammatory process in the disease.[7] There is also a known relationship between CSVV and autoimmune connective tissue diseases, and it is considered as the underlying cause in 15%–20% of the patients in the literature.[5] In this study, the laboratory parameters related to autoimmunity showed that 39% of the patients had ANA positivity, 20% had RF positivity, and 4% had ANCA positivity. These autoimmunity markers, which were detected in a large number of our patients, support the necessity to investigate and follow-up patients for autoimmune connective tissue diseases.

Vessel wall injury is related to immune complex deposition in CSVV.[6] In the literature, there are conflicting reports about the most common immune complex type in DIF.[6,8-11] In the study of Lath *et al*.,[10] DIF was positive in 60% of the patients, with the deposition of IgA being the most common, followed by C3. Nandeesh and Tirumalae[12] reported that 39% of patients were positive for DIF and they reported the most common immune complex subtype as C3, IgA, IgG, and IgM, in descending frequency. DIF positivities and the most common immune complex subtypes differ among different studies in the literature. In this study, the most common immune complex was C3 in 47% of patients, followed by IgA in 43%, IgM in 19%, and IgG in 6% of patients. There are many reports which indicate the close relationship between DIF positivity and timing of biopsy.[13-16] Because of the differences in the biopsy time and the faster dissipation of immunoglobulins compared to the complement, deposited immune -complex types were thought to differ between our study and other studies in the literature. C3 is expected to be deposited in late-stage lesions of vasculitis.[17] DIF findings are usually negative and unreliable in biopsies taken from older lesions of >48 h.[18] Therefore, early lesions should be preferred for biopsy. In this study, the age of the lesion, which was sampled, was not detected. This is one of the limitations which may have affected the DIF results. Another limitation is that it was not considered whether the biopsy site was exposed to the sun or not. It might have an effect on immune-complex depositions.[19] Biopsy site is also an important factor for stasis-related immune complex depositions.[20] IgA deposition can be detected in other dermatological diseases related to stasis,[20] but this limitation was not considered in the study when investigating DIF findings.

In our study, no statistically significant difference was found between DIF-positive and DIF-negative groups in terms of triggering factors, extracutaneous involvements, lesion localizations, and skin findings. There was also no statistically significant difference in the same parameters between immune-complex subtype groups. Takatu *et al*.[11] reported the association between IgM deposition and connective tissue disease or inflammatory comorbidities in LCV. In our study, laboratory parameters, including ANA, RF, ANCA, C3, and C4 levels, which are well-known autoimmunity markers,

Table 4: Comparison of laboratory findings according to immune complex subtypes in direct immune fluorescence positive group

Parameter	IgA			IgM			C3		
	Positive (%)	Negative (%)	*P**	Positive (%)	Negative (%)	*P**	Positive (%)	Negative (%)	*P**
Anemia	38	33	0.892	46	32	0.520	39	32	0.776
High WBC	28	36	0.413	23	35	0.560	29	35	0.447
High ESR	55	44	0.542	69	44	0.193	50	49	1.00
High CRP	69	69	1.00	100	61	0.006	69	70	1.00
High ASO	33	35	1.00	50	32	0.592	31	38	1.00
High creatinine	18	5	0.268	7	12	0.800	16	6	0.371
High transaminases	29	18	0.499	39	19	0.152	19	26	0.748
Low C3	9	6	0.811	18	5	0.341	12	3	0.420
Low C4	26	19	0.118	27	21	0.584	28	17	0.196
RF positivity	25	15	0.645	33	16	0.562	21	18	1.00
ANA positivity	46	34	0.592	42	38	1.00	40	38	1.00
AntidsDNA positivity	0	0	N/A	0	0	N/A	0	0	N/A
ANCA positivity	10	0	0.192	18	0	0.056	9	0	0.489
ENA positivity	0	0	N/A	0	0	N/A	0	0	N/A
HBV positivity	5	0	0.476	0	3	1.00	5	0	1.00
HCV positivity	0	0	N/A	0	0	N/A	0	0	N/A
Proteinuria	55	56	1.00	62	54	0.852	47	63	0.290
Hematuria	34	35	0.741	38	34	0.459	23	44	0.129
OBS	30	33	1.00	50	28	0.256	27	38	0.619

*Chi-square test or Fisher's exact test. N/A: Not applicable, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, ASO: Antistreptolysin O, C3: Complement 3, C4: Complement 4, RF: Rheumatoid factor, ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded DNA, ANCA: Anti-neutrophil cytoplasmic antibody, ENA: Extractable nuclear antigen, HBV: Hepatitis B virus, HCV: Hepatitis C virus, OBS: Ocult blood stool

were not statistically different between DIF-positive and DIF-negative groups. Takatu *et al*.[11] found a statistically significant difference with respect to ANA, SSA (anti-Ro)/SSB (anti-La) antibodies, C3/C4 levels, and IgM deposition and also with respect to ANCA and IgG deposition. Alalwani *et al*.[21] showed the correlation between DIF positivity and autoimmune markers, as well. Our study and contradictory data in the literature show that further studies are needed to elucidate the relationship between DIF findings and autoimmunity. In this study, no any association was found between extracutaneous involvement and DIF results, as in the study of Sais *et al*.[8] Unlike our results, Barnadas *et al*.[22] showed IgA deposition in patients with renal involvement and also, Alalwani *et al*.[21] detected IgA deposition in renal and GIS involvements. Takatu *et al*.[11] reported an association between C3 deposition and renal involvement, and between IgM deposition and autoimmune diseases. In our study, laboratory parameters, including blood creatinine levels, hematuria, spot or 24-h urinary proteinuria and OBS, showing renal or GIS involvement, were also not correlated with DIF findings.

The skin findings of this study were found to vary from petechiae, purpura, macule, and patch to more severe lesions, including papules, plaques, ecchymoses, bullae, and necrosis. No association between DIF findings and skin findings indicates that immune complex deposition does not affect the severity of skin lesions, and DIF findings cannot be predicted by lesion type.

It has been reported that the lesions located above the waist might be related to IgA deposition and organ involvement.[23] In this study, variable descriptions for skin findings and localizations were used. Because of the retrospective nature of the study, the objectivity of these variables might be limited. In addition to this limitation, there is a disequilibrium between the numbers of groups, which may lead to question the negative results of the study.

IgA deposition on DIF examination is an important diagnostic criterion for only HSP,[24] not for other vasculitis. This laboratory test should be requested to differentiate HSP from other small vessel vasculitis. Therefore, performing DIF examination only with IgA, not with other antibodies, fibrinogen, or complement, maybe enough for the diagnosis of HSP.

Conclusion

Based on the reports in the literature and our results, we think that DIF results did not play a role in determining the clinical findings and laboratory parameters in patients with CSVV. Therefore, the necessity of DIF examination, which is an expensive method, should be clarified with the prospective, large patient series.

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Conflicts of interest

There are no conflicts of interest.

References

1. Shinkai K, Fox LP. Cutaneous vasculitis. In: Bolognia JL, Schaffer JV, Cerroni L, editors. Dermatology. 3th ed. London: Saunders; 2012. p. 385-410.
2. Şahin EB, Hapa A, Elçin G, Karaduman A, Ersoy-Evans S, Erkin G, *et al*. Leukocytoclastic Vasculitis: Retrospective Analysis of 60 Patients. Turk J Dermatol 2011;5:85-91.
3. Calonje JE, Brenn T, Lazar A, McKee P, editors. Leukocytoclastic vasculitis. In: McKee's Pathology of the Skin. 4th ed. London, Saunders: Elsevier; 2011. p. 658-64.
4. Gru AA, Salavaggione AL. Vasculopathic and vasculitic dermatoses. Semin Diagn Pathol 2017;34:285-300.
5. Goeser MR, Laniosz V, Wetter DA. A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. Am J Clin Dermatol 2014;15:299-306.
6. Carlson JA, Ng BT, Chen KR. Cutaneous vasculitis update: Diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. Am J Dermatopathol 2005;27:504-28.
7. Ting TV. Diagnosis and management of cutaneous vasculitis in children. Pediatr Clin North Am 2014;61:321-46.
8. Sais G, Vidaller A, Jucglà A, Servitje O, Condom E, Peyri J. Prognostic factors in leukocytoclastic vasculitis: A clinicopathologic study of 160 patients. Arch Dermatol 1998;134:309-15.
9. Stone JH, Nousari HC. "Essential" cutaneous vasculitis: What every rheumatologist should know about vasculitis of the skin. Curr Opin Rheumatol 2001;13:23-34.
10. Lath K, Chatterjee D, Saikia UN, Saikia B, Minz R, De D, *et al*. Role of direct immunofluorescence in cutaneous small-vessel vasculitis: Experience from a tertiary center. Am J Dermatopathol 2018;40:661-6.
11. Takatu CM, Heringer AP, Aoki V, Valente NY, de Faria Sanchez PC, de Carvalho JF, *et al*. Clinicopathologic correlation of 282 leukocytoclastic vasculitis cases in a tertiary hospital: A focus on direct immunofluorescence findings at the blood vessel wall. Immunol Res 2017;65:395-401.
12. Nandeesh B, Tirumalae R. Direct immunofluorescence in cutaneous vasculitis: Experience from a referral hospital in India. Indian J Dermatol 2013;58:22-5.
13. Kulthanan K, Pinkaew S, Jiamton S, Mahaisavariya P, Suthipinittharm P. Cutaneous leukocytoclastic vasculitis: The yield of direct immunofluorescence study. J Med Assoc Thai 2004;87:531-5.
14. Grunwald MH, Avinoach I, Amichai B, Halevy S. Leukocytoclastic vasculitis–correlation between different histologic stages and direct immunofluorescence results. Int J Dermatol 1997;36:349-52.
15. Braverman IM, Yen A. Demonstration of immune complexes in spontaneous and histamine-induced lesions and in normal skin of patients with leukocytoclastic angitis. J Invest Dermatol 1975;64:105-12.
16. Gower RG, Sams WM Jr., Thorne EG, Kohler PF, Claman HN. Leukocytoclastic vasculitis: Sequential appearance of immunoreactants and cellular changes in serial biopsies. J Invest Dermatol 1977;69:477-84.
17. Johnson EF, Lehman JS, Wetter DA, Lohse CM, Tollefson MM. Henoch-Schönlein purpura and systemic disease in children: Retrospective study of clinical findings, histopathology and direct immunofluorescence in 34 paediatric patients. Br J Dermatol 2015;172:1358-63.
18. Sams WM Jr., Claman HN, Kohler PF, McIntosh RM, Small P, Mass MF. Human necrotizing vasculitis: Immunoglobulins and complement in vessel walls of cutaneous lesions and normal skin. J Invest Dermatol 1975;64:441-5.
19. Michel BA, Hunder GG, Bloch DA, Calabrese LH. Hypersensitivity vasculitis and Henoch-Schönlein purpura: A comparison between the 2 disorders. J Rheumatol 1992;19:721-8.
20. Helander SD, De Castro FR, Gibson LE. Henoch-Schönlein purpura: Clinicopathologic correlation of cutaneous vascular IgA deposits and the relationship to leukocytoclastic vasculitis. Acta Derm Venereol 1995;75:125-9.
21. Alalwani M, Billings SD, Gota CE. Clinical significance of immunoglobulin deposition in leukocytoclastic vasculitis: A 5-year retrospective study of 88 patients at Cleveland clinic. Am J Dermatopathol 2014;36:723-9.
22. Barnadas MA, Pérez E, Gich I, Llobet JM, Ballarín J, Calero F, *et al*. Diagnostic, prognostic and pathogenic value of the direct immunofluorescence test in cutaneous leukocytoclastic vasculitis. Int J Dermatol 2004;43:19-26.
23. Poterucha TJ, Wetter DA, Gibson LE, Camilleri MJ, Lohse CM. Correlates of systemic disease in adult Henoch-Schonlein purpura: A retrospective study of direct immunofluorescence and skin lesion distribution in 87 patients at Mayo Clinic. J Am Acad Dermatol 2012;67:612-6.
24. Linskey KR, Kroshinsky D, Mihm MC Jr., Hoang MP. Immunoglobulin-A–associated small-vessel vasculitis: A 10-year experience at the Massachusetts General Hospital. J Am Acad Dermatol 2012;66:813-22.