Vasculitides primarily involving the skin

Summary of the Ph.D. Thesis

GÉZA RÓBERT NAGY M.D.

Supervisor: Zsuzsanna Bata-Csörgő M.D., Ph.D., D.Sc.

Department of Dermatology and Allergology

Faculty of Medicine

University of Szeged

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LIST OF PUBLICATIONS

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II. **Nagy GR**, Veres K, Belső N, Németh IB, Varga E, Korom I, Kemény L, Bata-Csörgő Zs. Focal vascular occlusion: a link between livedoid vasculopathy and cutaneous polyarteritis nodosa? *Manuscript under review at J Am Acad Dermatol Int.*

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1. INTRODUCTION

1.1. Cutaneous vasculitis and its classification

The term vasculitis denotes inflammation of the blood vessel wall, which can occur in any organ system of the human body. In terms of blood vessel involvement, a stratification can be made in accordance whether the vasculitis affects the small, medium and the large-sized vessels of the arterial and/or the venous systems. Notably, certain vasculitides may have multiple vessel-type and/or size involvements resulting in a heterogenous clinical manifestation, often making the diagnostic process difficult. The very first International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC) was conducted in 1994. Since then, several advances have been made with regards to understanding the pathophysiological processes behind each vasculitis, which is reflected by the addendum to the CHCC held in 2012, where the discussion of skin-limited or skin-dominant forms was also necessitated. Additionally, the CHCC work group's definition of skin also includes the subcutaneous layer (therefore incorporating the medium vessels as well) and the mucosa, further widening the disease spectrum.

Vasculitis of the skin (cutaneous vasculitis) may be categorized into three different disease forms: 1) skin component of a systemic vasculitis (e.g., skin symptoms of a systemic IgA vasculitis); 2) skin-limited form of a systemic vasculitis (e.g., skin-limited IgA vasculitis); and 3) single-organ vasculitis of the skin (e.g., cutaneous polyarteritis nodosa). While the latter does not evolve into a systemic form of vasculitis, skin-dominant variants may do so. It should be noted however, that nonspecific symptoms of systemic inflammatory processes, such as elevated inflammatory markers, leukocytosis or arthralgia do not necessarily establish sufficient indication for the presence of a systemic involvement of said vasculitis. Hence, proper exclusion of the presence of clinically detectable non-cutaneous organ involvement is required to conclude whether the patient truly has a skin-limited vasculitis or a single-organ vasculitis of the skin.

Cutaneous vasculitides are characterised by inflammation of either the small vessels (including arterioles, capillaries and postcapillary venules) in the superficial and mid dermis and/or the medium-sized vessels (including smaller arteries and veins) located in the deep dermis or subcutaneous fat tissue. This locality of inflammation thus determines both the clinical and histopathological presentation of said vasculitides. Additional features, such as the presence or absence of systemic involvement, the quality of the immunoglobulin

deposition found with direct immunofluorescence staining and the presence of antineutrophil cytoplasmic antibodies add further criteria to be considered.

While multiple subclassifications are possible, the two major pathophysiological variants are antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immune complex-mediated vasculitis. As the clinical manifestations of ANCA-associated vasculitides show great heterogeneity, they may further be categorized based on their unique epidemiologic, pathologic and clinical features, in addition to their immunoserological findings, such as the presence of anti-proteinase 3 or anti-myeloperoxidase antibodies.

Immune complex vasculitides -as the name entails- are mediated by immune complexes, which first form in the presence of antigen and then later precipitate in antigen excess. Immune complex deposition primarily takes place in the dermal postcapillary venules, where inflammation is induced through the activation of the complement cascade, resulting in mast cell degranulation and neutrophil chemotaxis, thus it can also be histopathologically characterized as leukocytoclastic vasculitis. Proper skin biopsy sampling of the inflamed vessels increases the diagnostic yield, where the ideal timespan of the fresh cutaneous lesions is within the first 24 to 48 hours of its appearance. In the majority of cases a punch biopsy may suffice, however an incisional biopsy may be preferred, if the clinical manifestations suggest the involvement of the deeper, medium-sized vessels, such as in the appearance of necrosis or ulceration. Direct immunofluorescent staining of the cutaneous biopsy specimen shows deposition of either C3, IgA, IgG and/or IgM in a granular pattern within the vessel walls. The highest chance of detecting immunoglobulin deposition is performing a biopsy from a lesion that is present withing the first 48 hours. Of note, the evolution of the vasculitis may alter the qualitative features of direct immunofluorescent findings and can also result in its negativity. Hence, biopsy from a fresh lesion is essential for proper diagnostic workup. A key example for this was within the 2012 revised CHCC, where the denomination “Henoch-Schönlein purpura” was replaced by the term “IgA vasculitis”, owing to the compelling data indicating that IgA deposition proposes a unique pathophysiological feature of this vasculitis, segregating it from other immune complex-mediated forms.

1.2. Immunoglobulin A vasculitis and its systemic involvement

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is an immune complex-mediated small-vessel leukocytoclastic cutaneous vasculitis,

characterized by palpable purpura, accompanied by arthralgia or arthritis, gastrointestinal (GI) and renal involvement (also known as the “classic triad” of IgAV). While the exact cause of the disease is unknown, it is evident that the IgA systems has a key role in its pathophysiology, as serum IgA1 level elevation have been demonstrated in patients, owing to the increase in their production, disturbance in their clearance and their aberrant glycosylation. In most cases, the symptoms are usually benign and self-limiting in the acute stage, which can even resolve spontaneously, without a therapeutic intervention. However, in a small percentage of patients, severe systemic involvement may develop and life-threatening complications may occur, requiring aggressive treatment modalities. GI involvement may precede the onset of purpuras, presenting with colicky abdominal pain and/or GI bleeding. These symptoms are cause by bowel ischemia and oedema, which may further proceed into infarction or perforation. Renal involvement occurs in approximately 40-50% of patients, presenting with microscopic hematuria, which may be accompanied by proteinuria. Of note, nephritis may have a prolonged development timespan, compared to the cutaneous lesions, and can also be clinically detectable within 3-6 months as well. The distinction between IgAV with nephritis and IgA nephropathy should be made, despite their clinical similarities. Both entities are characterized by hematuria, proteinuria and immune complex deposition in the glomerular mesangium. The main differentiator for the two is that while IgA nephropathy is restricted specifically to the kidneys, IgA with nephritis is part of the clinical spectrum of a systemic involvement. IgAV is often regarded as a disease of childhood with an annual incidence rate of 3-26.7/100.000, but contrary to popular belief, it is not uncommon in adults. Although it is considered to be the same entity, the clinical manifestations and disease course differ greatly in these two age groups. Previous studies have demonstrated that unlike in children, adult patients develop systemic involvement more frequently, with a high risk of severe GI bleeding and chronic kidney disease. This highlights the importance and the need of prognostic markers that can help identify IgAV patients who are at risk of developing unfavorable extracutaneous manifestations.

While predictive factors have been extensively studied in children, there is limited data on adults. Blood neutrophil-to-lymphocyte ratio (NLR) is an inexpensive and easily obtainable laboratory marker for quantifying systemic inflammation, which has been used to predict clinical outcomes in patients with various internal malignancies, cardiovascular disease and liver cirrhosis. As this ratio integrates information on two immune pathways, it may provide a predictive ability that outweighs other inflammatory parameters. Despite the

strong prognostic potential of NLR in the aforementioned diseases, particularly in certain malignancies, no biopsy-proven IgAV studies have been conducted among the adult population. In this matter, if NLR harbors adequate prognostic potential in IgAV, it may serve as not only a valuable biomarker in clinical decision making but a tool for patient risk stratification.

1.3. Cutaneous vasculitis and vasculopathy

In addition to the stratification of a "skin-limited" variant from a "systemic vasculitis with a skin component", another subject arises. In clinical practice, distinguishing vasculitis from vasculopathy is also a constant challenge, often leaving one contemplating whether thrombosis was secondary to the inflammation of the blood vessels or vice versa. Although current knowledge advocates segregation by means of histopathological examination, it may not grasp the whole underlying pathomechanisms, due to disease evolution, which may also explain the discrepancy seen in the literature regarding this question. Hence, one might consider the notion that owing to such underlying dynamic pathomechanisms, both vasculitis and vasculopathy may complementarily coincide with one another, and that diagnostic stratification based on histopathology alone may not grasp the full scope of the condition at hand. As such, rather than segregating thrombosis and inflammation, we should perhaps consider them as integrants of a framework, encompassing both vasculitis and vasculopathy. Of peculiar interest, livedoid vasculopathy (LV) and cutaneous polyarteritis nodosa (CPAN) stand in the precipice of such a differential diagnostic challenge, where histopathology provides the distinction between the two entities.

LV is an uncommon skin disease, characterized by focal vascular occlusions in the form of non-inflammatory thrombosis of the dermal venules, resulting in ulcerations and Milian's atrophie blanche. The denomination "atrophie blanche" has long been used as both a descriptive term for ivory-white scars on the lower limbs, thought to be a result of chronic inflammation and microvascular occlusion and also as a diagnostic term in the case of LV. Notably, LV was initially described as a clinical manifestation of vasculitis, however, at present time, the main pathogenic mechanism driving it is considered to be vaso-occlusive processes, primarily deriving from intraluminal thrombosis. This notion is supported by the vast body of literature describing the positive therapeutic effects of fibrinolytic, antiplatelet therapy and anticoagulants in LV. A number of publications have advocated the concept of LV being a cutaneous manifestation of certain prothrombotic processes, rather than a unique pathology in itself. Therefore, a broad number of diseases have been associated with LV

through the disturbance of the Virchow's triad. Due to the heterogenous etiology and wide differential diagnosis of LV, histopathological examination is essential. The histopathological features of LV are characterized by occlusion of the superficial and/or middle dermal vessels by fibrin deposition, intravascular thrombosis, segmental hyalinization and endothelial proliferation, all in the absence of vasculitis. Notably, deep cutaneous biopsies are necessary, as there are cases presenting with symptoms and histopathologic features suggestive of LV, but are actually the manifestations of CPAN.

CPAN is a skin-limited necrotizing vasculitis, affecting the small and medium sized arteries in the dermal-subcutaneous junction, resulting in the aforementioned "atrophie blanche" skin symptoms. Notably, the classification schemes of polyarteritis nodosa (PAN) and other vasculitides have changed as our knowledge of their aetiopathogenesis evolved over time, also allowing for more specific treatment modalities in these disorders. The term necrotizing vasculitis is now regarded as a feature of a wide variety of diseases with different etiologies, which include classic PAN, microscopic polyangiitis (MPA), granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome).

Although CPAN predominantly affects the skin, extra-cutaneous symptoms may arise, such as fever, myalgias, arthralgias and neuropathy. While the first signs of systemic PAN may be the cutaneous lesions seen in CPAN, upon extensive clinical screening, multi-organ involvement is apparent, particularly in the kidneys, heart, GI tracts and the liver, hence the distinction between the two is essential. While the etiopathogenesis of CPAN is still unclear, it is regarded as a disorder mediated by immune complexes, where direct immunofluorescence often shows C3 and IgM deposition. Intriguingly, previous studies described the presence of IgM antibodies targeting the phosphatidylserine-prothrombin complex in patient with CPAN, which would then lead to the activation of the classical complement cascade. On this note, the connection to prothrombotic processes have also been made, where warfarin therapy has been reported to be effective in the treatment of adult CPAN patients. To date, however, the conceptualization of thrombotic vs. inflammatory processes in LV and CPAN still continues to be perplexing.

2. AIMS

Distinguishing a skin-limited variant of a vasculitis from its systemic form with a skin component before signs of internal involvement, grants an upper hand in therapeutic management, resulting in a lower risk of potential complications and mortality. To search for indicators in this matter, we examined adult patients with IgAV. IgAV is a small-vessel leukocytoclastic cutaneous vasculitis, often associated with kidney and GI manifestations. Although predictive factors for systemic involvement have been extensively studied in children, there is paucity in the literature regarding adults. NLR is an inflammatory marker, used to assess systemic inflammation in various diseases.

I. Our aim was to evaluate whether NLR can predict and determine the presence and severity of the systemic involvement in adult IgAV patients, hence differentiating skin-limited IgAV from systemic IgAV with a skin component, while also providing prognostic practicality (Study I.)

Though cutaneous biopsy remains an indispensable tool for diagnostic workup in the segregation of vasculitis and vasculopathy, clinical experience leaves us with controversy, without a definite etiopathological line distinguishing the two. LV and CPAN are rare cutaneous diseases of currently unknown etiologies. To date, the concept of thrombosis vs. inflammation in these entities continue to be ambiguous, with varying reports on the effectiveness of anticoagulant and immunosuppressant therapies.

II. Our aim was to assess the presence of vasculopathy in adult patients with CPAN, with the added notion of LV and CPAN being constituents of a clinical evolution of focal vascular occlusion (Study II.)

3. MATERIAL AND METHODS

3.1. Patients

Study I. A retrospective review of adult patients diagnosed with IgAV between January 2004 and January 2016 was performed. Patients needed to have palpable purpura consistent with the disease, skin biopsy specimen showing leukocytoclastic vasculitis on light microscopy and IgA deposition on direct immunofluorescence. Patients were excluded if they had an immunologic comorbidity, coexisting internal malignancy, hematological disorder, cryoglobulinemia or any chronic renal or GI diseases. Additionally, patients who experienced hematochezia, melena or hematemesis two days before or after blood sampling, were also excluded owing to the possibility of neutrophilia being the secondary effect of an acute hemorrhage.

Study II. A retrospective study of eight patients with CPAN was conducted, who were treated at the Department of Dermatology and Allergology, University of Szeged, from 2010 through 2018. The diagnosis of CPAN consisted of histopathological findings of necrotizing vasculitis of the small and medium-sized arteries at the dermal and subcutaneous junction, in addition to presence of clinical manifestations in accordance with CPAN, without any signs suggestive of systemic involvement. We then compared our data with those found in the literature regarding the clinical, histopathological and prothrombotic laboratory parameters of LV, to determine whether prothrombotic processes may serve as a common ground in the etiopathology of CPAN and LV.

3.2. Data collection

Study I. We analyzed the medical records and registered the following: gender, age, duration of symptoms before blood sampling, clinical symptoms, results of laboratory testing and initial treatment. The laboratory test results included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), neutrophil and lymphocyte counts, hematological parameters, urine and stool examinations. NLR was calculated based on the initial complete blood count test, by dividing the neutrophil count with the lymphocyte count. By reviewing the ambulatory records, we also registered any subsequent renal or GI symptoms following initial remission. Patients were followed from baseline visit until loss of follow-up or death.

Study II. Regarding the medical records of CPAN cases, we recorded the age of onset of the disease, gender, duration of symptoms, clinical symptoms, notable medical history

with concomitant medications, histopathologic features, initial treatment and laboratory data, which included the immunoserological and thrombophilia screening panel. To further assess the presence or absence of certain cutaneous symptoms of the disease, we revised an electronic photo documentation database, available at our institution, which prospectively enrolls patients.

3.3. Assessment of GI and renal involvement in IgAV

We defined GI involvement as clinical signs of hematochezia, melena or hematemesis, or a positive test result for fecal hemoglobin. Renal involvement was determined through hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen; in the absence of concurrent urinary tract infections, urolithiasis and anticoagulant therapy) or proteinuria (>150 mg/24h), or presence of predominant mesangial IgA deposition on the renal biopsy specimen.

4. RESULTS

4.1. Predictors of systemic involvement in adult IgAV patients (Study I.)

4.1.1. Basic characteristics of the study sample

Forty adult patients with IgAV who met the inclusion criteria were identified. The median age was 61 years (range 19-82 years). The cohort included 23 (57.5%) females and 17 (42.5%) males. Half of the patients had clinical symptoms suggestive of GI and/or renal involvement, of which 6 (15%) had only renal, 3 (7.5%) had only GI and 11 (27.5%) had both renal and GI involvement. Patients received initial treatment after blood sampling and in all cases either corticosteroid monotherapy or a combination of corticosteroid and antibiotics were employed. Based on the severity of the subsequently developed renal and GI symptoms, therapies were altered accordingly at the discretion of the clinician.

4.1.2. Clinical features

As NLR represents an inflammatory response, we also included other routinely used inflammatory markers for comparison. Spearman correlation analysis indicated a significant correlation of NLR with CRP (ρ=0.482; p=0.002), ESR (ρ=0.37; p=0.019) and WBC (ρ=0.469; p=0.002), however no significant correlation was observed with the duration of symptoms before blood sampling (ρ=-0.269; p=0.094) or patient age (ρ=0.282; p=0.078).

When stratifying patients based on their renal and GI manifestations and comparing the inflammatory laboratory parameters, there were no statistically significant differences, irrespective of which organ involvement the patients had, thus the enrolled cases were divided into two groups.

While group 1 included patients who only had cutaneous symptoms, group 2 consisted of patients who developed GI and/or renal manifestations of IgAV, in addition to the cutaneous symptoms. Of the registered inflammatory markers, CRP (p=0.002) and NLR (p<0.001) were significantly higher in group 2, whereas the other laboratory parameters, age, gender and the duration of symptoms were not statistically associated with systemic involvement.

Six (30%) patients in group 2 displayed GI involvement with the presence of macroscopic bleeding, whereas eight (40%) only had fecal hemoglobin positivity without a clinically apparent hemorrhage. With regards to renal symptoms, proteinuria was a frequent finding among those with a systemic involvement (n=15; 75%), however none of the patients

developed nephrotic syndrome. In two patients, renal involvement progressed into end stage renal disease, 11 and 14 days following initial blood analysis.

4.1.3. Receiver operating characteristic curves of NLR versus other inflammatory markers

ROC curves of NLR and other inflammatory markers in relation to the systemic involvement were performed. The area under the curve (AUC) for NLR, CRP, ESR and WBC was 0.892 (95% CI: 0.785-1; $p<0.001$), 0.779 (95% CI: 0.635-0.922; $p=0.003$), 0.669 (95% CI: 0.498-0.839; $p=0.068$) and 0.637 (95% CI 0.462-0.813; $p=0.089$), respectively. Of the considered laboratory data, NLR provided the strongest diagnostic value, as indicated by the highest AUC value. The optimal cut-off value of NLR for predicting systemic involvement was 3.34, with a specificity of 95% and a sensitivity of 85%.

4.1.4. NLR and disease severity

We examined the correlation of NLR and disease severity in patients with renal and/or GI involvement by constructing a simple 7-point scoring system based on the clinical manifestations and course of the disease. Patients received 1 point for each of the following features: hematuria, proteinuria, renal impairment, fecal hemoglobin positivity, macroscopic bleeding from the GI tract, the necessity of intensive care / surgery / dialysis or blood transfusion and death. NLR was found to be significantly correlated with the disease severity score ($\rho=0.51$; $p=0.022$).

4.2. Assessing the presence of vasculopathy in adult CPAN patients (Study II.)

4.2.1. Clinical characteristics

A total of eight cases were reviewed in the series. The 5 male and 3 female (M:F ratio, 1.6) patients had a median age of 46 (range, 24–68 years) at diagnosis. The median duration of the relapsing symptoms before cutaneous biopsy sampling was 36 months (range, 2–240 months).

The clinical manifestations consisted of purpura in 4 (50%), erythematous papules or plaques in 7 (87.5%), subcutaneous nodule in 1 (12.5%), livedo racemosa in 7 (87.5%), cutaneous ulcer in 7 (87.5%) and atrophie blanche in 7 (87.5%) cases. Without exception, the skin symptoms were always localized to the lower extremities, with notable predilection for the ankle regions. All cases were screened for antinuclear antibodies, ANCAs and complements, with negative results.

4.2.2. Histological features

In all cases, deep skin biopsies containing the subcutis were obtained. Each specimen displayed hyalinized dermal blood vessels, perivascular neutrophilic and lymphocytic infiltrate, leukocytoclasia and marked narrowing of the vessel lumens. Notable thrombosis was not apparent in most cases (87.5%), with only one specimen displaying extensive thrombosis in the papillary and deep dermis. Fibrinoid deposition in the papillary and deep dermal vessels was present in 7 (87.5%) patients. Direct immunofluorescent staining showed complement deposition in the vessel walls in 8 (100%) cases, with IgA in 4 (50%) and IgM in 4 (50%) cases.

4.2.3. Coagulation disorders

Procoagulative conditions were found in 7 (87.5%) patients. Elevated levels were detected of fibrinogen in 2 (25%), antithrombin III in 2 (25%), homocysteine in 1 (12.5%), factor VIII in 3 (37.5%) cases. Protein S deficiency was detected in one (12.5%) patient and the lupus anticoagulant screening test was positive in 3 (37.5%) cases, without increased values in anti-cardiolipin or beta-2-glycoprotein antibodies.

4.2.4. Therapeutic regimen

Initial therapies consisted of corticosteroids, however 3 (37.5%) patients required alteration in their immunosuppressants within a median of 4 months (range, 1.3-4.6 months). Subsequently, only partial response was achieved long-term (median, 12 months; range, 7.2-58.1 months), thus, in consideration of the procoagulative parameters, warfarin therapy was initiated in all cases. All patients responded favourably to anticoagulation. Three cases remained asymptomatic with warfarin monotherapy alone.

5. DISCUSSION

Although IgAV is often a self-limiting and benign disease in children, severe complications may occur in adults, including renal impairment and serious GI bleeding, requiring intensive care or surgery. In order to gain more prognostic information, we examined the utility of a noninvasive and easily obtainable cost-effective laboratory parameter. To our knowledge this is the first biopsy-proven case-control study to investigate the predictive value of NLR for systemic involvement in adult IgAV patients.

Half of the patients included in Study I. developed renal and/or GI involvement, of which the majority concurrently had both organs affected. When stratifying patients based on their renal and GI involvement and comparing the registered laboratory results, there were no significant differences in the hematological and the inflammatory laboratory values, which implies that NLR and the other inflammatory markers are not organ specific prognostic indicators and their elevated values were not the secondary effect of an underlying severe bleeding. Consequently, the high NLR observed in our study, is therefore likely to be the result of an inflammatory response.

Our results demonstrated that out of all the considered inflammatory parameters, NLR had the strongest diagnostic value. The optimal cut-off point for predicting systemic involvement was 3.34 with a specificity of 95% and a sensitivity of 85%. Additionally, we also found that pretreatment NLR values significantly correlated with the severity of the disease in patients who developed systemic involvement.

Progression to end stage renal disease was observed in two individuals. Compared to children, adult IgAV patients are more likely to present with a delayed renal involvement, often requiring close monitoring and diligent testing for even up to 6 months. While delayed renal involvement was not observed in any of our cases, it should be noted that 20 patients (10 individuals from group 1 and 10 individuals from group 2) did not have a follow-up time period of at least 6 months. Although one of the patients with a lower NLR than the cut-off value identified in our study developed renal manifestations of IgAV during his admission, he remained asymptomatic throughout the follow-up time period (9 years).

More than a third of our patients had GI involvement, which in most cases consisted of colicky abdominal pain with fecal hemoglobin positivity. Severe complications, such as intussusception and perforation were also observed in two cases, the latter resulting in a fatal outcome. None of the patients in our cohort with a lower NLR value than 3.34 displayed any

clinical signs suggestive of GI involvement, during their admission and follow-up, which further highlights the prognostic value of NLR.

As our selection was based on both clinical and histopathological findings, with the exclusion of patients with other background diseases, we believe our data represent accurate observations. There seems to be reasonable potential for this marker as a tool for clinical risk stratification at the time of IgAV diagnosis, thus also allowing for a more patient-specific therapeutic intervention.

On the matter of the vasculitis and vasculopathy conundrum, we examined the clinical features of a single-organ vasculitis of the skin, focusing on the presence of procoagulative components of the disease.

Presently, CPAN is considered to be a necrotizing vasculitis and although its etiology is not fully elucidated, current concepts advocate that it is mediated by immune complex deposition. Likewise, the pathogenesis of LV also lingers on uncertain grounds, though, the interpretation of non-inflammatory thrombosis of the dermal vessels remains to be widely accepted. Contrariwise, reports of LV and CPAN not responding to the conventional treatments, leave us with controversy regarding the aforementioned concepts. Additionally, despite the presumed difference in their underlying pathomechanisms, these two entities share notable clinical similarities not only in their cutaneous manifestations but also in their recurrent and usually non-progressive clinical courses, implicating a link amongst their pathophysiological mosaics.

In Study II. the cutaneous manifestations of CPAN were compatible with LV in all cases, with pain being a constant subjective symptom. Additional manifestations of the series included peripheral neuropathy in two of our patients, which has also been described in LV. No evidence of autoimmune abnormalities were detected in our series, thus excluding other forms of vasculitis or rheumatologic diseases.

Histological features of our study sample displayed segmental hyalinizing vasculitis, with intravascular deposition of fibrin and secondary changes deriving from vascular occlusion. Perivascular lymphocytic infiltrate, in addition to neutrophils, was a prominent feature in our cases, which is also often seen in LV. Albeit extensive intraluminal thrombosis, characteristic of LV, could only be seen in one of our cases, it is commonly described in CPAN alike. Whilst LV initially appears with a histopathologic picture showing fibrin thrombi without evidence of inflammation, it is later presented as hyalinized fibrin

rings with lymphocytic infiltrate, signs of vasculitis and erythrocyte extravasation, accompanied by neutrophilic infiltrate and immunoglobulin deposition. Additionally, while superficial skin histopathology may show vessel occlusion identical to LV, they are secondary changes to the inflamed vessels in the deep dermis, thus, superficial biopsies can be misleading in CPAN, which may also explain the discrepancy in the literature.

Similar to a hypercoagulable state seen in LV, we found coagulopathies in the majority (87.5%) of our patients, giving a considerable role for anticoagulant therapy in CPAN as well. While immunosuppressives are the mainstay, long-term management of our patients necessitated the introduction of anticoagulative treatment, with good therapeutic response. Although cutaneous biopsy provides essential morphological insights, it is also important to consider the clinical experience and therapeutic responses, hence, we believe a considerable role should be given to the vasculopathic aspects of CPAN, in addition to vasculitis, which may serve as a common ground for widening our scope of the vasculopathy vs. vasculitis question.

Lastly, the accentuation of thrombosis and inflammation going hand-in-hand must be noted as more evidence comes to light regarding the intricate connection between the innate immunity and the coagulative cascade, a pathomechanism which has been termed immunothrombosis. When activated, neutrophils are capable of releasing neutrophil extracellular traps (NETs), which are comprised of DNA matrix, harboring histones, nucleosomes and neutrophil elastase. NETs are considered to be crucial structural factors in the formation of immune-elicited thrombi, as they promote the intrinsic coagulation pathway. Previous studies have also demonstrated that these processes occur in autoinflammatory disorders, in the absence of microbial pathogens. Owing to these mechanisms, increased prevalence of thrombosis has been observed in several other autoimmune diseases.

In closing perspective, the clinical experience should compose a crucial factor in addition to the histopathological examination throughout the frameworks of the diagnostic workup. The significance of recognizing the presence of both vasculitis and vasculopathy is underlined by the good therapeutic effect of the employed treatment modalities in our described cases. Of point, even in situations where the dominant feature of the clinical presentation is inflammation, procoagulative aspects need to be taken into consideration as part of the thrombotic continuum enveloping both hemostasis and immunothrombosis.

6. CONCLUSIONS

I. Our results suggest that NLR is a potential prognostic marker for systemic involvement in adult IgAV and can be used to identify patients at risk of developing extracutaneous manifestations.

II. We also found that increased pretreatment NLR correlated with the severity of the systemic involvement, which may aid in the stratification of patients into risk groups.

III. In addition to vasculitis, the vasculopathic aspects of CPAN should be recognized as well, giving a considerable role for anticoagulative therapy. Though histopathological assessment regards CPAN as a vasculitis, clinical experience suggests a more complex underlying pathomechanism, where vasculitis and vasculopathy may be intertwined throughout a dynamic clinical evolution.

IV. Further prospective studies on mapping the disease stages of focal vascular occlusion, with CPAN in its focus, should broaden the horizon and help us elucidate the full scope of the underlying pathomechanism.

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