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Looking Beyond the Cutaneous Manifestations of Covid 19, Part 2: The Pathology and Pathogenesis - A Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

This is the second part of the article, titled "looking beyond the cutaneous manifestations of Covid 19 Part 1: The Clinical Spectrum – A Review", which is exclusively relegated to the pathology and pathogenesis aspects. The cutaneous manifestations of Covid 19 are classified into four broad groups, from the pathology and pathogenesis point of view and the histopathology of all the cutaneous lesions are briefly reviewed. The role of vasculitis and endothelitis in the pathogenesis of skin lesions in Covid 19, are discussed. The vasculitis and thrombotic microangiopathy (TMA) are discussed at length as they occupy the centre stage of pathogenesis, in the literature, at present. The various types of vasculitis reported in literature, are classified on the basis of skin lesions seen and the rationality of the various terms used in the context of the pathogenesis are explained. It is stressed that that the central players in the pathogenesis of skin lesions in Covid 19 are, vasculitis, activation of complement pathways and coagulation cascade and the cross- talk between the two at various points in their respective pathways. For the details of the complement activation, activation of coagulative cascade and for the details of the role of innate and adaptive immunity

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system, the readers may refer to the author's previous article titled "Local Immunity Concept in the Context of the Novel Corona Viral Infection- A Consideration." *** (reference of which is provided under the additional information at the end of the article). Some contentious issues concerning the role of the vasculitis and immune complex mediated damage, of the vessel wall in the pathogenesis of cutaneous lesions of Covid 19, are discussed. A non-immune, non-vasculitis, alternative mechanism is suggested by floating a two hit hypothesis. The necessity to apply the rigours of diagnostic criteria of vasculitis is emphasized to get a standard picture of the histopathology and pathogenesis of cutaneous manifestations of Covid 19 by future research.

Keywords: Vasculitis; thrombotic microangiopathy; MAC complex; coagulation cascade; complement activation.

1. INTRODUCTION

No single mechanism, perhaps explains all the dermatological manifestations of Covid 19. For example, the localized acral lesions like, the Covid toes, histologically resembles primary chilblain (perniosis) histopathology, and the pathology and pathogenesis of exanthematous truncal lesions like vesicular and papular types etc. are no different from that of any other viral disease. The levidoid and necrotic lesions, Which are seen in critically ill, elderly Covid 19 patients, resemble the pathology of the lungs in Covid 19. Even the ICD-10 classification of the skin diseases classifies "vasculitis limited to skin" under "L", category and "necrotizing vasculopathies "corresponding to systemic vasculitis, with musculoskeletal system and connective tissue conditions under "M" category (ICD10 data.com). It shows that the local as well as systemic versions of the same disease are considered as distinct entities. By the same anolgy, localised lesion like Covid toes, is a distinct entity and levidoid and necrotic skin lesions, which are associated with simultaneous systemic involvement affecting the lungs and kidney etc, have separate and distinct pathologies. The levidoid / necrotic lesions can be viewed as the forerunners of a coagulopathy in the fatal cases of Covid 19 disease involving multiple viscera .There is no unanimity of the opinion, as to whether the pathology of the cutaneous lesions is due to direct infection by the SARS CoV 2 or due to the dysregulated host immune response. The inflammatory injury of the intima of the small sized blood vessels (vasculitis) perhaps explains the pathology of Covid toes with the subsequent activation of the coagulation cascade accounting for the microvascular thrombosis that characterizes the levidoid/necrotic lesions and the concurrent severe lung pathology as well – the two shot concept of pathogenesis of cutaneous manifestations seen in Covid 19. The central theme of the pathogenesis of the skin lesions in Covid 19, seems to be activation of coagulative cascade pathways (extrensic and contact pathways) and the complement activation pathways (alternate pathway, MBL pathway and the classical pathway) with a cross talk between the two. The two interacting pathways (coagulative and complement activation) are fully discussed in the article published under th title "Acute Immune Mediated Lung Injury in COVID 19: A Review" *(for details at the end of the article) by this author. Hence discussion will be centred on the cross talk between the two systems. Likewise, the clinical and epidemiological spectrum of the various cutaneous manifestations of Covid 19 are discussed by this author in the article, titled "Looking Beyond the Cutaneous Manifestations of Covid 19- Part 1: The Clinical Spectrum" ** (details athe end of the article.) To avoid repetition the article proceeds directly with the pathology and pathogenesis of the cutaneous manifestations in the present article. The interested readers may refer to the part 1 of this series, for the detailed description of these aspects of the skin lesions of Covid 19**(vide infra, under additional article information). Unfortunately, unanimity is lacking among the authors as to the pathology and pathogenesis of the cutaneous lesions of Covid 19.The final word on the pathology and pathogenesis of these lesions as a whole, is yet to be said. So, no readymade answers to the issues under consideration may be expected as the article intends to review the reported views in n the literature in this regard and makes an attempt to rationalize them.

2. DISCUSSION

From the point of view of pathology and pathogenesis, the cutaneous lesions are classified by this author into 4 broad groups (Table 1).

2.1 Diagnostic Value and Limitations of Histopathological (HP) Studies of Cutaneous Lesions in Covid 19

The cutaneous lesions are diagnosed clinically, basing on their morphological presentation Histopathological (HP) study is confirmatory to clinical diagnosis, where a known pattern associated with a disease is known. The Covid 19 pandemic is, of recent origin and the cutaneous lesions have come under scrutiny only from the end of April, 2020. There is no standardized histopathology data available before the pandemic .The percentage of skin lesions seen, in Covid 19 patients are as such few, out of which only a handful of studies by researchers focussed on biopsy and HP studies. Among1099 confirmed cases in Wuhan, only 0.2% presented with cutaneous symptoms. So a review of the histological details of various skin lesions of Covid 19 is limited to few authentic studies. The recently reported lesions such as, dengue-like lesions, Kawasaki disease -like lesions as well as paediatric Multisystem Inflammatory Disease are severely handicapped by lack of HP studies. As such it is not surprising if the reviewers draw a blank in this regard. On the other hand, the HP studies aid in understanding the disease from pathogenesis point of view.

2.2 Histopathology of Covid Toes

The histopathology of Covid toes on one hand resembles that of primary perniosis and on the other hand, it has to be differentiated from the secondary perniosis, like cutaneous polyarteritis nodosa (c PAN) and sub acute cutaneous lupus erythematosus (SCLE) and Lupus pernio. Primary or idiopathic perniosis result of vasospasm of the superficial vasculature and secondary inflammatory reaction [1]. It is usually associated with cold temperatures and vasospasm [2]. Secondary perniosis are associated with systemic inflammatory conditions. Histopathology of Covid toes shows dermal edema and a lymphocytic perivascular and perieccrine inflammatory infiltrate. Occasional necrotic keratinocytes and focal areas of basal vacuolization may be seen in the epidermis. No microvascular thrombi are seen.Very recently Kolivras et al. [3] reported the first histopathology of a chilblain like lesion showing a superficial infiltrate and deep lichenoid, perivascular and perieccrine infiltrates of lymphocytes without any thrombi.

2.3 Similarity with Histopathology of Primary Perniosis

The salient features of periniosis are-“Dense superficial and deep lymphocytic infiltrate, Subepidermal oedema may be marked. The characteristic feature is lymphocytic perivascular infiltrate within the dermis and sometimes extending to the sub cutis” (DerNet NZ) Dense superficial and deep lymphocytic infiltrate within the dermis and sometimes extending to the sub cutis, are similar to chilblains suggesting a possible link between the two. This was thought to represent “lymphocytic vasculitis”. The most characteristic finding in chilblains in 47% of cases was the association of oedema and reticular dermis infiltrate that showed a perieccrine reinforcement. 52% of cases showed necrotic keratinocytes in the epidermis (Aram Boada. 2010 [4]. Subacute Lupus Erythematosus (SCLE) is more likely to show a widespread

Table 1. Classification of cutaneous lesions based on pathology and pathogenesis

1.	**Lesions showing features of vasculitis only:**	
	a.	*Covid toes.*
	b.	*Acute urticarial lesions.*
2.	**Lesions showing features of vasculitis, coagulopathy and complementopathy.**	
	a.	*Levidoid lesions.*
	b.	*Necrotic lesions*
	c.	*Haemorrhagic lesions*
3.	**Lesions showing non-specific features similar to those in any other viral diseases:**	
	a.	*Morbilliform lesions.*
	b.	*Papular lesions.*
	c.	*Pityriasis like lesions*
	d.	*Vesicular lesions. (varicella-like lesions)*
4.	**Lesions mimicking other specific diseases:**	
	a.	*Dengue-like lesions.*
	b.	*Kawasaki-like lesions.*
	c.	*Lesions seen as a part of Paediatric Multisystemic Inflammatory Syndrome.*

vacuolar interface with scattered necrotic keratinocytes in the lower part of the epidermis and is less likely to show perieccrine lymphocytic infiltration and significant dermal oedema [5,6].

Differential Diagnosis of the Covid Toes Pathology:

2.4 Cutaneous Polyarteritis Nodosa (c PAN)

Fibrinoid necrosis with thickening and infiltration of the vessel wall is characteristic of c PAN. Thrombi and aneurysmal change may be present Vessel occlusion occurs secondary to intimal and mural fibrosis. Lack of oedema and the presence of vacuolation were more characteristic of lupus erythematosus.

2.5 Lupus Pernio

Lupus pernio with its red to manifestation p urple or violaceous indurated plaques and nodules may resemble the Covid toes, clinically, but its distribution beyond the acral parts especially affecting the nose, cheeks, ears, and lips is unmistakable [7]. The word lupus pernio is a misnomer as it has nothing to do with lupus In fact it is a of cutaneous sarcoidosis which is considered a CMI response to an unknown antigen. The pathogenesis involves autoimmune dysregulation with activation of the Th1 immune pathway resulting in release of cytokines like IL2, TNF alfa and interferon gamma, aided by T regulatory cells (Tregs). Histologically it is characterised by noncaseating epithelium cell granuloma with giant cells and histochemestry demonstrates the CD4+ Th1 lymphocytes.

Chilblain lupus erythematosus (CHLE) is a form of cutaneous lupus erythematosus that presents with lesions of similar morphology and distribution to primary pernio [8]. Biopsy of CHLE show findings similar to idiopathic pernio with superficial and deep perivascular lymphocytic infiltrates; however, CHLE is more likely to show a widespread vacuolar interface with scattered necrotic keratinocytes in the lower part of the epidermis and is less likely to show perieccrine lymphocytic infiltration and significant dermal oedema [9,10]. Chilblain-like lesions of leukemia may have acral presentation but the peripheral smear examination will distinguish it from Covid toe [11].

2.5.1 Pathogenesis of Covid toes

Covid toe is considered as a sign of good immunity while others consider it as an epiphenomena unrelated to Covid 19 infection.

A study found a direct relation between Covid toe and SARS CoV 2. [12].

2.5.2 Vasculitis vs endothelitis

Presence of eosinophils in the dermal infiltrate and the high positivity rate of direct immunofluorescence examination, highlights the involvement of vascular injury in the genesis of these lesions.

Presence of endothelialitis in chilblain-like lesions is consistent with a role of the SARS-CoV-2 because endothelialitis in several organs has been reported in the course of COVID-19 [13].

2.5.3 Morbilliform like rash [14]

Maculopapular eruptions show superficial perivascular dermatitis with slight lymphocytic exocytosis, swollen thrombosed vessels with neutrophils, eosinophils and nuclear debris/superficial and deep perivascular dermatitis with cuffs of lymphocytes surrounding blood vessels.

2.5.4 Papular lesions of Covid 19: Histopathology

It shows perivascular vesicular dermatitis, focal acantholytic suprabasal clefts, dyskeratotic and ballooning, herpes-like, keratinocytes and swollen vessels with dense lymphocyte infiltration mixed with rare eosinophils in the dermis [15]. In some cases it was perifollicular and associated with scaling and confluence, which might cause it to be mistaken for pityriasis rosea **(pityriasis rosea -like lesions)**. But the typical distribution and histopathology of PR will be wanting in Covid 19 papulosquamous eruptions.

2.5.5 Pityriasis rosea-like lesions

“Biopsy revealed mild diffuse epidermal spongiosis, spongiotic vesicles containing lymphocytes, and Langerhans cell.The papillary dermis was slightly oedematous. In the upper dermis, a lymphohistiocytic infiltrate was noted.” [16].

2.5.6 Vesicular type of rash in Covid 19 [17]

Prominent non-ballooning acantholysis leading to the constitution of an intraepidermal unilocular vesicle, with in two patients a clear suprabasal location eosinophilic dyskeratosis was also constant, with on occasion a striking 'pomegranate-like' aspect features more suggestive of a viral infection were present once. No vasculitis was seen. The direct immunofluorescence performed in one patient and the two SARS-CoV-2 PCR tests performed on vesicles were negative. The rash that we observed was similar to that reported by Marzano, and constituted a picture that we agree to be evocative of COVID-19. But, in addition, the histologic pattern of prominent acantholysis and dyskeratosis with constitution of an unilocular intraepidermal vesicle in a suprabasal location, reported here for the first time, contributed to delineate a unique entity. Indeed, this pattern is very different from what is seen in varicella, in which major nuclear atypia, large multinucleated cells, acantholysis secondary to ballooning degeneration, involvement of the epidermis basal layer and vasculitis are regularly seen. Other acantholytic disorder (autoimmune or familial pemphigus, Grover's transient acantholytic dermatosis) do share some histologic features with our cases, but with a distinct clinical context.

2.5.7 Urticarial lesions – histopathology: [18]

Eriko Itoh et al. (2020) described the histopathology of urticarial rash in general,which is cited as comparison with those described in Covid 19.

The histopathological features of urticaria are dermal edema and perivascular and interstitial inflammatory cell infiltration, and minimal change in the epidermis. Cellular infiltrates are composed of lymphocytes, neutrophils, and eosinophils. Urticarial lesions show perivascular infiltrate of lymphocytes, some eosinophils and upper dermal oedema. Urticarial vasculitis lesions show blood extravasation and neutrophilic perivascular inflammation with prominent karyorrhexis, some macrophages with a cytoplasm full of nuclear debris and endothelial swelling, necrosis and fibrin deposition. Some urticarial lesions show slight vacuolar-type interface dermatitis with occasional necrotic keratinocytes with no eosinophils, consistent with an erythema multiforme-like pattern (Kaya and Kaya et al).

Other reports show extensive fibrin deposition in the vessel walls, surrounding the vessels is a mixed infiltrate predominately composed of neutrophils with leukocytoclasis. Early lesions show a perivascular neutrophilic infiltrate involving post capillary venules. The histologic pattern associated with hypocomplementemic type, is interstitial neutrophilic infiltrate of the dermis and an immunofluorescent pattern of immunoglobulins or C3 in the blood vessels and along the basement membrane zone. Acute urticaria has an increase in IL-6, PCR, and d-dimer.

2.5.8 Petechial and purpuric rash

Skin biopsy disclosed superficial perivascular lymphocytic infiltrate with abundant red cell extravasation and focal papillary edema. The epidermis showed focal parakeratosis and dyskeratotic cells. There were no signs of thrombotic vasculopathy [19].

2.5.9 Livedoid and necrotic lesions in Covid 19

These lesions are premonitory of impending doom to the patient as they are seen mostly is severely ill, PCR positive Covid patients in ICU, with associated severe Covid 19 pneumonia. The laboratory parameters are also seen to be in tune with the gravity of the condition with elevated fibrinogen, D-dimers and inflammatory markers like CRP etc.

2.5.10 Histopathology of livedoid vasculopathy in Covid 19 [20]

The salient features are

- Variable necrosis of the epidermis. Dilated blood vessels in dermis containing hyaline thrombi
- Neutrophilia with infiltrate in perivascular distribution.
- Fibrinoid necrosis.

For comparison the Levidoid vasculopathy as seen in non-Covid 19 patients is shown below.

2.5.11 Histology of levidoid vasculopathy

Fibrin occlusion and thrombus formation involving the upper and mid-dermal capillaries. There is hardly any perivascular inflammatory infiltrate, but when present, the infiltrate is predominantly lymphocytic. Extravasation of red blood cells results from vessel wall damage. Neutrophil infiltration and leucocytoclasia are usually absent In the stage of atrophie blanche, there is hyalinization of the dermis and capillary walls. Defects either in the endothelial cell plasminogen activation, platelet dysfunction or

enhanced fibrin formation are considered factors behind the thrombotic phenomena.Pericapillary deposition of fibrin and formation of thrombus act as a diffusion barrier impairing tissue oxygen supply causing ischemic infarction. Low tissue perfusion leads to poor wound healing.

2.5.12 Livedo reticularis-like lesions in Covid 19

Livedo reticularis-like vascular lesions have been reported in a few patients with COVID-19. [21,22] with laboratory-confirmed diagnosis.

2.5.13 Livedo racemosa like lesions in Covid 19 (Retiform purpura)

Retiform purpura and necrotic vascular lesions seem to be associated with severe COVID-19 [23,24]. In a series, nine out of 11 patients with retiform purpura and laboratory confirmed COVID-19, had acute respiratory distress syndrome. Histologic and immunohistochemistry studies of skin biopsies revealed a pattern of complement-mediated microvascular injury in both involved and normally appearing skin. Histopathological findings of thrombotic vasculopathy was observed.

2.5.14 Dengue like lesions –histopathology [25]

Histopathological examination showed hemorrhage, perivascular edema and focal necrosis but no vasculitic or endothelial lesions. It is believed that most of the morphologic abnormalities seen result from disseminated intravascular coagulation and shock.

2.5.15 Kawasaki-like lesions histopathology

Kawasaki-like presentation during the COVID-19 pandemic among children is reported; In many cases, RT PCR for SARS 2 is negative and the association with COVID-19 infection is unclear [26]. Fibrin thrombin in smaller vessels with patchy infarcts (Am J Surg Pathol 1982;6:493) skin lesions in Kawasaki disease (KD) have been characterized by extensive edema associated with the dilatation of small vessels in the papillary dermis. The infiltrate was mainly monocytic [27]. The infiltrating cells in the dermis and epidermis were mainly composed of CD 3+ T cells and Leu M3+ macrophages, but not B cells. In double immunofluorescence staining with combinations of anti HLA-DR, CD4 and CD8 monoclonal antibodies, the infiltrating T cells were mainly CD4+ HLA-DR+ T cells. The skin lesions in KD appear to be similar to those found in delayed type hypersensitivity. Thus, macrophages and helper T cells may play a crucial role in the pathogenesis of KD [28].

2.5.16 Histopathology of thrombotic microangiopathy (TMA)

Fogo, Agnes, Bruijn,et al summed up the histopathology of TMA as follows; [29]

- Microvascular occlusion.
- "Loose" intimal thickening; fluffy appearing intima.
- May be have an onion skin-like appearance.
- Fibrin entrapped RBCs .
- The last two are useful for discrimination from endarteritis [7].
- Early finding: endothelial cell swelling.

At the outset the definitions of some terms that the reader may come across in this article are tabulated below.

Table 2. Definition of some terms used in the pathology and pathogenesis

Vasculopathy	A general term used to describe any disease affecting blood vessels [1]. It includes vascular abnormalities caused by degenerative, metabolic and inflammatory conditions, embolic diseases, coagulative disorders, and functional disorders such as posterior reversible encephalopathy syndrome.
Coagulopathy	Broadly defined as any derangement of hemostasis resulting in either excessive bleeding or clotting, although most typically it is defined as impaired clot formation. This includes disseminated intravascular coagulation. From: Handbook of Clinical Neurology, 2017.
Complementopathy	Defined as a disorder in which: (1) activation of the complement system is a driving factor in the disease pathophysiology, and (2) there is evidence that inhibition of complement disrupts or halts the pathogenic process of the disorder.
Vasculitis	It means inflammation of the blood vessel. (The matter is discussed more in details, vide infra)

Table 3. Histological patterns relevant in the context of Covid 19 infection

Pattern associated with mainly inflammation and no thrombosis	
a.	*Leucocytoclastic vasculitis*
b.	*Lymphocytic vasculitis*
Patterns associated with inflammation and vascular	
a.	*Lymphocytic thrombophilic arteritis*
b.	*Thrombotic occlusive vasculopathy*
c.	*Thrombotic microangiopathy (TMA)*
d.	*Levidoid vasculopathy (LV)*
Pattern associated with thrombosis without evidence of inflammation	
a.	*Thrombotic occlusive vasculopathy*
b.	*Thrombotic* microangiopathy

2.5.17 Vasculitis: its role in cutaneous lesions of Covid 19

The term vasculitis simply means inflammation of the blood vessel. Mere presence of inflammatory infiltrate in the vessel wall is not enough as the same can occur during the diapedesis and chemotaxis [30]. Essential to the confirmed histological diagnosis of vasculitis is demonstrating the evidence of inflammation--induced damage to the vessel wall, like deposition of fibrin or necrosis of the vessel wall or thrombosis of the lumen of the blood vessel. Some of these changes may be seen late in the course of the disease, in which case histological criteria may change as the disease advances. The diagnosis of these vasculitis should bear clinico-pathological correlation. It is necessary to state the type or caliber of the blood vessel involved ie. The small / medium or large blood vessel (Chapel Hill Consensus Nomenclature (CHCC), modified in 2012) [31,32] the histological picture varies according to the type of blood vessel involved. It is helpful to decide whether it is an endovasculitis with an intact internal lamina (true to small vessel vasculitis) or transmural, involving the muscle layer of the blood vessel (c PAN). The predominant type of inflammatory infiltrate, is also important, whether it is neutrophilic (leucocytoclastic vasculitis) or lymphocytic infiltrate (lymphocytic vasculitis).Final outcome of the vessels involved is also is important i.e. whether ther is fibroid necrosis of the vessel wall (as in c PAN) or thrombotic occlusion of the blood vessel. (Thrombotic/thrombophilic vasculitis). It is observed that the above criteria are strictly not observed in cases of reported histopathology of cutaneous manifestations of Covid 19 and some authors just refer the underlying pathology as vasculitis without even histological backup study.

2.6 Small Vessel Vasculitis

It presents as localized cutaneous vasculitis or as a systemic disease. It is either primary /idiopathic or secondary (due to infections, drugs, collagen disease or malignancy or auto immune disorders it may be localised or systemic, involving many viscera. [33]. Covid toes, is considered as a localised vasculitis. The levidoid/necrotic lesions are usually associated with lungs, kidney etc and represents a systemic vasculitis. Kenar D. Jhave Lea R. Meir et al described a case of small vessel vasulitis in Covid 19 [34].

Diagnostic criteria [35] should be fulfilled before accepting a diagnosis is accepted.

- The blood vessel involved should be a capillary, post capillary or arteriole.
- The predominant infiltrate should be neutrophils.
- Presence of leukocytoclasis, which refers to vascular damage caused by nuclear debris from infiltrating neutrophils.
- Evidence of destruction of the vessel wall by the infiltrating neutrophils, in the form of fibrin deposit or fibrinoid necrosis.

There seems to be some relaxation to these criteria. cellular infiltrate is leucocyte, a term which doesn't restrict to neutrophils alone but it could be any other type of leucocyte like the lymphocytes, basophils, eosinophils or even monocyte. And that leukocytoclasis is a feature of inflammation not necessarily restricted to LCV. The presence of fibrinoid necrosis demonstrated in a small blood vessel is accepted as proof of small vessel vasculitis, even in the absence of other features. Again, the word 'arteritis' is used closely to refer to the small vasulitis though it should be reserved for the medium and large

blood vessels. Fibrinoid necrosis is also seen in c PAN with which LCV can be confused but identifying a medium sized blood vessel as well as vessel wall damage evidenced by nodose lesions distinguish the later. Thus when LCV is ascribed, to a new entity like Covid 19 and more so in case of Covid toes, unless the absolute criteria are satisfied histologically, any other basis for the same would be unacceptable. The existing evidence in the literature should be viewed critically as more reported incidents fall short of these criteria [36].

Small vessel vasculitis is anonymously used as LCV but it includes group as seen below.

2.6.1 Histopathology of LCV: [37]

Histologically, LCV is characterized by leukocytoclasis, which refers to vascular damage caused by nuclear debris from infiltrating neutrophils. LCV classically presents as palpable purpura. Less common clinical findings include urticarial plaques, vesicles, bullae, and pustules [34].

2.6.2 Mimickers of vasculitis: [38]

Some vaso-occlusive conditions, characterized histologically by thrombi within the lumen or fibrin without accompanying inflammation. Examples include disseminated intravascular coagulation (DIC), APLA syndrome, dysgammaglobulinemia and embolic phenomena. They do not fulfil the criteria for vasculitis.

ANCA-associated systemic vasculitis (AASV) are a group of diseases classified as small vessel vasculatides that are associated with anti-neutrophil cytoplasmic antibodies. AASV include microscopic polyangiitis, Wegener´s granulomatosis, Churg-Struass syndrome and renal limited vasculitis. Cutaneous vasculitis of Covid toes is ANCA negative [39].

2.7 Lymphocytic Vasculitis

It is a histological diagnosis characterised by the presence of lymphocytes attacking a small vessel, endothelial swelling with or without fibrin deposition. Perivascular dermatitis with vasculopathic change is another name suggested. Vasculopathic reaction pattern refers to pathologic changes in blood vessels like endothelial swelling and inflammation with extravagated erythrocytes. Clinically heterogenous diseases like connective tissue disease, infection, lichenoid diseases, drug reaction, Behçet's disease, superficial thrombophlebitis and leukemic etc exhibit this type of vasculitis. Even idiopathic pernio is considered a type of lymphocytic vasculitis. Covid toe pathology is likened to that of primary perniosis. Three forms of lymphocytic vasculitis are reported.Angio-destructive form, lichenoid lymphocytic vasculitis and lymphocytic endovasculitis. Angiodestructive form is usually seen in lymphoproliferative disorders. Lichenoid form is seen in inflammatory skin diseases as part of the pathologic features which are often characterized by lichenoid vacuolar change and erythrocyte extravasation. Endovasculitis ahead of thrombosis in obliterative conditions. It presents both in localised as well as systemic form. The prognosis in the localised form is favourable and the lesions heal but the process may linger an year or so (some authors describe it as chronic and indolent). It is described as a distinct entity than LCV anx palpable purpura is not discribed in this type as well as leukocytoclasis or fibrinoid necrosis characteristic of LCV. Clinically it presents as hives, red or purplish discoloured patches, a nodule, or an ulcer have all been described as symptoms of this condition. The size, location, and severity of symptoms varies widely among affected individuals. IN the systemic form there would be symptoms as per internal organ affected [40]. A detailed description of the lymphocytic vasculitis can be had from the article of M. C. Aydin, Ozay Gokoz. Lymphocytic Vasculitis: Classification of 127 cases [41].

2.8 Lymphocytic Thrombophilic Arteritis

Lee JS, Kossard S, McGrath MA et al. [42] termed this arteritis *lymphocytic thrombophilic arteritis* to reflect the histologic features that combine lymphocytic vascular inflammation with changes representing a thrombophilic endovasculitis. Young female patients, with a median age of 39 years are effected. Robert I Kelly Edmund Wee Chasari (July 2020) [43] reported 3 cases of lymphocytic thrombophilic vasculitis It is a primary lymphocytic endovasculitis clinically associated with livedo racemosa or macular hyperpigmentation and histologically by localized thrombophilia, characterized by the intraluminal fibrin ring without any evidence of destruction of the vessel wall [44]. Some cases have been associated with autoimmune antibodies or heterozygosity for prothrombotic mutations, suggesting that autoimmunological and thrombophilic factors may contribute. **Antiphospholipid antibodies**

have been detected in some cases, but the low titres and lack of systemic features argue against antiphospholipid syndrome contributing significantly to its pathogenesis.

Low to moderate levels of antinuclear antibodies (ANA) have been reported, but there was no evidence of systemic connective tissue disease in these cases .The infiltrate was predominated by lymphocytes and handy nistocytic. The intimal elastic lamina was intact in most cases. It is a unique form of C5b-9 mediated arthritic endotheliopathy where the brunt of the changes involves the endothelium and intima and that is morphologically distinct from the transmural arteritis of benign cutaneous Poly arteritis nodosa (cPAN). There is up regulation of type I interferon and inducible interferon gamma 16 protein. it may represent an indolent non–nodule-forming variant of cutaneous polyarteritis nodosa (cPAN).

2.8.1 Histopathology

Dense inflammatory infiltrate is found in the muscular vessel wall, affecting the small and medium-sized arteries of the deep dermis, junction of the dermis and sub cutis, or superficial subcutis.

The inflammatory infiltrate consists predominantly of mononuclear cells, mainly lymphocytes and some histiocytes.

Neutrophils and eosinophils are scant or absent.

A concentric hyalinised fibrin ring involves the entire periphery of the Lumina of the affected vessels. Signs or symptoms of systemic vasculitis are also absent.

4. Thrombotic occlusive vasculopathy in a skin biopsy from a livedoid lesion of a patient with Covid 19:

M. Llamas-Velasco reported a case of livedoid purple lesions along with acrocyanosis in a patient confirmed for SARS-CoV-2 infection. intensive care unit with a diagnosis of COVID-associated severe bilateral pneumonia complicated with diabetic ketoacidosis. The patient presented with Persistent livedo racemosa of the lower limbs, Palpable subcutaneous indurations occasionally ulceration [45,46]. The authors call the histopathological picture as. Thrombotic occlusive vasculopath Showed a slightly necrotic upper epidermis. The papillary dermis, showed dilated blood vessels filled with hyaline thrombi and a few with a mild neutrophilic component surrounding tthem.Dermo–hypodermal interface showed focal fibrinoid necrosis surrounded by a scarce neutrophilic infiltrate Sweat gland necrosis and degeneration were present, more evident in the secretory portion of the eccrine sweat coil, with preserved eccrine ducts. Polymerase chain reaction for SARS-CoV-2 from the skin biopsy was negative. M. Alonso-Riaño (20th June 2020) demonstrated C5 b-9 deposits in the dermal vasculature by histochemical methods and immunofluorescent techniques in a series if 7 cases, in one case they could show the presence of the SARS CoV 2 with the help of electron microscopy. Suggestive of a viral exanthema a biopsy from the buttocks showed features consistent with a thrombotic vasculopathy [47,48].

2.9 Occlusive Nonvasculitic Vasculopathy

Clinically, most of these conditions are characterized by retiform purpura. Histopathologic findings consist of occlusion of the vessel lumina with no vasculitis or inflammatory infiltrate. Some of the systemic coagulopathies reported to have been characterised by this type of vasulitis are defects of C and S proteins, coumarin / warfarin-induced skin necrosis, disseminated intravascular coagulation, ant phospholipid antibody/lupus anticoagulant syndrome.

2.10 Haemorrhagic and necrotic skin lesions due to heparin use

It is not uncommon that heparin prophylaxis is given to those critically I'll Covid 19 patients who are at increased risk for DIC Such patients may develop usually 5 to 7 days after starting heparin, painful erythematous, haemorrhagic / necrotic lesions at the site of injection or at distant places. biopsy of the necrotic plaque edge, stained with haematoxylin and eosin, demonstrates intravascular thrombi throughout the dermal vasculature in the absence of any significant inflammatory cell infiltrate (Occlusive Nonvasculitic Vasculopathy).

2.11 Thrombotic Microangiopathy (TMA)

TMA describes a specific pathologic lesion in which abnormalities in the vessel wall of arterioles and capillaries lead to microvascular thrombosis [49,50]. The triad of thrombocytopenia, schizocytosis in the blood

smear and an increase in LDH level distinguish this from Covid 19 coagulopathy. Endothelial activation causes sticky platelets, resulting in the formation of platelet thrombi in the micro circulation. These micro thrombi are responsible for hypo perfusion of the organs affected and also the hemolytic anemia, caused by mechanical destruction. Gavriilaki and Brodsky reviewed the thrombotic microangiopathy (TMA) associated with COVID 19, noting that TMA appears to be more a complement-mediated thrombotic microangiopathy, rather than that due to sepsis-induced coagulopathy or disseminated intravascular coagulation (DIC) [51].

The different entities of TMA bear similarity in histopathology, but are distinguishable by the epidemiological, clinical and laboratory features.

2.11.1 Type of TMA relevant to the context of Covid 19

Table 4 shows the Classification of TMA.

2.11.2 TTP Vs HUS

HUS (haemolytic-uremic syndrome) and TTP (thrombotic thrombocytopenia purpura) are usually considered part of clinical spectrum, in which disease manifestations depend on distribution of microangiopathy) [52].

While TTP involves Heart, brain, adrenal gland and pancreas, HUS does not involve any of these viscera.

The predominant consumption of platelets, with evidence of minimal fibrinogen depletion, and the platelet-derived nature of the microvascular lesions, characterize TTP. HUS mainly occurs in children and is preceded by e coli/shigella enteritis and kidney failure is very severe. In addition to classic TMA findings, HUS typically presents with bloody diarrhea, fever, and hypertension. TTP typically presents with fever, hypertension, mild proteinuria, and neurologic symptoms.

2.11.3 Atypical HUS

It is due to excessive complement activation in microvasculature; inherited and acquired abnormalities affecting components of the alternative complement pathway are found in 60% [53].

2.11.4 Covid coagulopathy vs DIC

Intravascular micro thrombi, thrombocytopenia and vascular endothelial damage occur in both conditions [54]. Rarely patients with severe COVID-19 infection and multiorgan failure progress to a coagulopathy meeting criteria for overt DIC as per International Society on Thrombosis and Haemostasis (ISTH) criteria. [55].

- platelet count <50 x109/L),
- prolongation of the PT and aPTT,
- extreme elevation of D-dimer,
- and decreased fibrinogen (< 1.0 g/L).1.

2.11.5 Covid coagulopathy vs TMA coagulopathy

TMA coagulopathy is distinguished from Covid coagulopathy by:

- Low platelet count with normal clotting factors.
- Mild to moderately low red blood cell count
- hemolytic anemia
- schistocytes in a blood smear

But patients with severe COVID-19 infection and multiorgan failure progress to a coagulopathy meeting criteria for overt DIC per ISTH criteria, reflected by

- moderate to severe thrombocytopenia (platelet count <50 x109/L),
- Prolongation of the PT and aPTT,
- extreme elevation of D-dimer,
- and decreased fibrinogen (< 1.0 g/L).1.

Table 4. Classification of TMA

S. no	Type
1.	Thrombotic Thrombocytopenic purpura (TTP).
2.	Haemolytic uremic syndrome (HUS).
3.	Complement-mediated TMA (also called atypical HUS; aHUS).
4.	Secondary TMA.
5.	SIRS – (Systemic inflammatory response syndrome)
6.	DIC -- (Disseminated intravascular coagulation)

2.12 Histopathology of TMA

It is characterized by primary damage to the vascular endothelial cells. The endothelium initially becomes detached from the underlying basement membrane and the sub endothelial space is filled with amorphous material and fibrin. Within the vascular lumen, there are platelet-fibrin thrombi that can completely occlude the vessel. Fibrin predominates in HUS and platelets are more prominent in patients with TTP (8) [56]. +/-onion skin-like appearance (chronic change).

2.12.1 TMA vs Vasculitis

Vasculitis is differentiated by presence of the following which are not seen in TMA

- Inflammatory cells within the vessel wall.
- Vessel wall injury, i.e. necrosis.

2.12.2 Livedoid vasculopathy

It may be questioned as to what levidoid vasculopathy has to do with cutaneous lesions of Covid 19?

2.12.3 Levidoid vasculopathy Vs levidoid lesions of Covid 19

- As already seen some researchers mention, livedoid vasculopathy-like lesions in Covid 19, as seen already
- Both the diseases share the histological feature of thrombosis of microvasculature resulting in tissue hypoxia, with consequent low tissue perfusion
- The leg ulcers and the consequent healing with the typical stellate, porcelain atrophic scars called 'atrophie blanche' which appear in due course, but not in Covid 19. Pericapillary deposition of fibrin and formation of thrombus act as a diffusion barrier impairing tissue oxygen supply causing ischemic infarction
- In Covid 19, the levidoid lesions are seen in the seriously ill patients. Well before the leg ulcers and atrophie blanche lesions make their appearance, the patient with Covid 19 might die. This is from the authors view point.
- Pericapillary deposition of fibrin and formation of thrombus act as a diffusion barrier impairing tissue oxygen supply causing ischemic infarction. The severity of lesions may not be that severe to cause tissue infarction, leg ulcers formation and the consequent typical scar as seen in LV.
- Some insights might be gained from the pathogenesis of livedoid vasculopathy which could help understand the pathogenesis of Cutaneous lesions of Covid19, like-
- Defects either in the endothelial cell plasminogen activation, platelet dysfunction or enhanced fibrin formation are considered as factors behind the thrombotic phenomena, in levidoid (LV).
- The link between coagulation and inflammation is exemplified by the fact that protease-activated Plasminogen -1 present on endothelium induces pro-inflammatory cytokine secretion (interleukin-6, interleukin-2, monocyte chemo-attractant protein-1) and adhesion molecule expression (intercellular adhesion molecule-1, P-selectin). This promotes leukocyte diapedesis and contributes to the inflammatory response.

Other procoagulant factors considered in coagulopathy of levidoid vasculopathy, that might have bearing in levidoid lesions of Covid 19.

- Hyper-cysteinemia: The normal serum homocysteine concentration ranges between 5 to 15 µmol/L. Levels higher than this are associated with livedoid vasculopathy [57,58].
- Activated protein C resistance is the more common inherited cause of thrombophilia associated with livedoid vasculopathy. [59,60].
- Increased protein C levels: The heterozygous deficiency of this protein with functional. Levels <65% is associated with an increased risk of thrombotic events which improves with antiplatelet treatment [61,62].
- Increased level of plasminogen activator inhibitor and low level of tissue plasminogen activator activity (<0.03 IU/mL) [63].
- Auto antibodies and antiphospholipid syndrome; Demonstration of antibodies to cardiolipin and phospholipid in levidoid vasculopathy make it possible that it could be manifestation of a autoimmune disease.

2.12.4 Micro thrombi in cutaneous vasculature: The pathophysiology

Micro thrombi in the cutaneous vascular is seen, as already mentioned, in patient's presenting

haemorrhagic/levidoid / necrotic lesions and simultaneously with those in the pulmonary vasculature. It is not clear whether the skin lesions are secondery to more common pulmonary pathology or is a local manifestation in the dermatological lesion consequent to the hyper coagulation state prevailing. Some consider the cutaneous lesions are a manifestation of thrombo embolic phenomena consequent to pulmonary vascular thrombosis. This distinction should have bearing on the pathogenesis at the level of the lung and skin. The response of different organs may be different to the same insult. Hence the discussion is limited to what applies to thrombosis of cutaneous vasculature than as an over view of a unified pathology. The pathology and pathogenesis is discussed by this author “Acute immune mediated lung injury “else where of acute IT here may be overlap in the pathology in both the organs and may also may have differences due to local milieu. The pathogenesis cite the demonstration of the viral particles in the vessel wall. The infection induced endothelitis alters blood vessel barrier integrity, promotes pro-coagulative state, induces vascular inflammation and mediates inflammatory cell infiltration. It Inhibits coagulation by expressing coagulation inhibitors and blood clot-lysing enzymes and producing a glycocalyx (a protective layer of glycoproteins and glycolipids) with anti-coagulation properties ECs are enriched in transcriptomic signatures indicating immunoregulation5, maintains vascular integrity and barrier fun.

2.12.5 Role of Endothelitis

ACE2 receptors are also expressed by endothelial cells. The endothelial injury can be caused directly by the SARS CoV 2, apoptosis, pyrolysis or as a fallout of the immune response of the body to the virus. The demonstration of viral particles both by immuno chemistry and electron microscopy lends support to direct infection of the endothelium by the virus. The endothelial injury can attract inflammatory cells and intimate coagulation process. Through TF or platelet activation. The MAC complex deposited on the endothelium of cutaneous vasculature can not only helps apoptosis but also the coagulation-complement cross talk.

2.12.6 Clotting and thrombus formation under physiological conditions

The interactions between the complement system and hemostatic factors maintain hemostasis under physiologic conditions and promote thrombosis under the pathologic conditions. In both a platelet thrombus (which is due to activated sticky platlets formed under the coordinated action of the activated complement system), forms. In hemostasis it is formed when blood leaks out of the blood vessel and it's role is protective sealing the rent in the vessel wall to arrest further bleeding. The inhibitors of clotting - protein C and protein S, antithrombin and tissue factor pathway inhibitor (TFPI), prevent blood from clotting unless, hemostatic factors are recruited. Further sequences of full pledged clot formation starts when the TF on the musculo endothelial cells is exposed to blood, containing factor 7 and V, the completing of which activates by extrinsic pathway, the factor X into Xa which perpetuates the further cascade till prothrombin is converted to thrombin and thrombin converting fibrinogen into fibrin. The fibrin clot is stabilized by factor X111.

2.12.7 Pathological Clotting/ thrombosis in COVID-19

The pathological, intravascular clotting in Covid 19 occurs because of the activated complement system (through the alternate and lectin pathways as well as the classical pathway) and activated coagulation cascade (by extrinsic and intrinsic or contact cascade and possibly through inhibition of the Protein C-protein S pathway.) and the cross talk between them. This author, extensively reviewed the role of all the above pathways as well as role played by innate and adaptive immune systems role of the vascular endothelium, the macrophage polymorphism elsewhere*(see below under additional article information).In this article the discussion is limited to the cross talk between the complement and coagulative pathways. This aspect has been extensively reviewed by. Jonathan H.Fole, Edward M. Conway. Cross Talk Pathways Between Coagulation and Inflammation (2016) [64].

2.13 The Anaphylatoxins

The C3a and C5a produced in the complement activation pathway are called anaphylatoxins.

- C3a and C5a induce endothelial cells to express IL-8, IL-1, and RANTES (Regulated upon Activation, Normal T Cell expressed and Presumably Secreted) is a chemokine secreted by platelets that have been activated predominantly during flow conditions.

- C3a and C5a recruit and activate innate immune cells, such as monocytes, neutrophils, and macrophages and inducing changes in endothelial permeability [65].
- C5a also triggers exposure of cell adhesion molecules such as P-selectin. These act as inflammatory mediators facilitating the adhesion of neutrophils to the endothelium.
- C5a increases tissue factor (TF) activity in both circulating form and on endothelial cells [66].
  - Causes Increased expression of PAI-1 on mast cells PAI-1 is a serine protease inhibitor (serpin) that functions as the principal inhibitor of the tissue plasminogen activator (tPA) and urokinase (uPA), the activators of plasminogen and hence fibrinolysis (the physiological breakdown of blood clots).

MAC (membrane activation complex) /TP (terminal protease) complexes:

TP complexes (C5b-7, C5b-8, and C5b-9) also activate cells, causing the production of inflammatory mediators (reviewed by Morgan). Complement directly induces a prothrombotic phenotype through

- C5a: TF expression on neutrophils and endothelial cell
- C5b-7: TF expression on monocytes, von Willebrand factor secretion from endothelial cells [67].
- C5b-8/C5b-9-mediated platelet activation [68].

2.14 MASP-1 (Mannose Associated Serine Protease) and MASP-2

These are, a group of serine proteases that initiate the lectin complement pathway, can cleave prothrombin to form activated thrombin and autonomously activate fibrinogen and factor XIII (fibrin stabilizing factor) [69,70].

2.15 Complement System Inhibitors

They are also able to inhibit the coagulation cascade [71]. C1 esterase inhibitor (C1-INH) can inhibit factor XII [72] and thrombin [73], and C4b-binding protein (C4BP) has been shown to inhibit protein S, a co-factor for the activated protein-C pathway of coagulation inhibition. Thus, the complement system is capable of activating the coagulation cascade.

2.16 Tissue Factor (TF)

TF expression is rapidly upregulated and de-encrypted in

1. Response to chemical or physical damage
2. Inflammatory cytokines (TNFα IL-1β)
3. Infectious agents
4. Oxygen-free radical etc.

Complex with circulating factor VIIa, triggering coagulation by activating coagulation factors IX and X.

When the amount of thrombin generated exceed a threshold beyond negative regulatory influences to promote platelet activation, fibrin clot formation, and a myriad of proinflammatory events, occur. The latter are mediated via activation of PAR cell signaling pathways.

2.17 Protein C and S

Activated protein C exerts its anticoagulant activity primarily through inactivation of coagulation factors Va and VIIIa, which are required for factor X activation and thrombin generation. The catalytic activity of activated protein C is greatly enhanced by the vitamin K–dependent cofactor protein S.3. The function of protein S is to inactivate factor Va and factor VIIIa. This function is carried out directly by protein C and protein S serves as a cofactor.

Table 5. Cross talk between complement and coagulation pathway

Complement side	Coagulation side
1. Anaphylatoxins (C3a and C5a)	1. TF
2. MAC (C5-9 Complex)	2. EC
3. Complement inhibitors	3. Platelets
4. MASP-1 and. MASP-2	4. Protein P
5. (Lectin pathway)	5. Protein S
	6. Thrombin
	7. Fibrinolytic system.

2.18 Thrombin

On the inflammatory side, thrombin can also activate PAR-1 on endothelial cells and fibroblasts to trigger production of monocyte chemoattractant protein-1, TNFα, and IL-1β, and IL-6 [74,75]. PAR-1-dependent signaling also causes endothelial cells to become activated, resulting in P- and E-selectin exposure and expression of monocyte chemoattractant protein-1, IL-8, plasminogen activator inhibitor-1 (PAI-1), and IκB-β. Together, these endothelial effects mediate platelet and leukocyte recruitment and adhesion and rolling on the endothelium, which are processes known to occur during the early stages of venous thrombosis [76]. Adherent leukocytes and platelets are susceptible to PAR-mediated activation, resulting in IL-6 and IL-8 production by fibroblasts and monocytes [77] and increased platelet effects described earlier. Altogether, these processes form a potent positive feedback loop that amplifies inflammation and procoagulant processes at the vascular surface.

2.18.1 Complement and fibrinolysis

1) C1-INH in its native state was found to inhibit plasmin [78] which could lead to decreased fibrinolysis and increased thrombus formation.

2) Complement factors have been shown to stimulate the expression of plasminogen activator inhibitor-1 (PAI-1) by mast cells, further inhibiting fibrinolysis and thereby presumably promoting thrombosis.

3) MASP-1 is able to activate thrombin-activated fibrinolytic inhibitor (TAFI) an inhibitor of fibrinolysis.

2.18.2 Complement and platelets

1. P-selectin, a platelet alpha granule membrane protein is an activator of the alternative complement cascade on platelets [79].
2. Platelet alpha granules contain Factor D, the serine protease that cleaves Factor B of the alternative pathway to its active form Davis 3rd, and Kenney [80].
3. Platelets express binding sites for classical complement components, C1q. C1q interactions with platelets trigger a variety of cellular and biochemical responses that may contribute to inflammation and thrombosis.
4. Platelets activate and regulate the complement system via assembling complement-activating protein complexes and expressing or anchoring complement regulatory proteins on their surface.5-MAC is able to activate platelets and enhance platelet aggregation [81,82,83] in the binding of coagulation factors Va and Xa, which increases platelet prothrombinase activity and initiates the release of the prothrombotic factor V from alpha-granules [84,85].

2.18.3 Some contentious issues

It is not yet settled, whether the pathology and pathogenesis of cutaneous lesions of covid 19 are due to direct endothelial infection by the SARS CoV 2 infection or due to immune response mounted by the body in defence against the invading virus. Though electron microscopy detected SARS CoV 2 virus in the microvasculature of skin, whether it represented the whole virus or fragments of it is not settled. Also, the virus multiplication or otherwise in the endothelium is also debated.

Table 6. Rigorous criteria for diagnosis of small blood vessel vasculitis

1. Demonstration of vessel wall damage by any or most of the criteria cited below.	a) Fibrinoid necrosis. b) Fibrin deposit in the vessel wall. c) Predominant cell (neutrophil/ lymphocyte/monocyte etc) in the Inflammatory exudate attacking the cell wall d) Bleeding into the vessel wall e) Extravasation of RBC outside the vessel wall.
2. Leucocytoclasia and nuclear dust	
3. Clinico-pathological correlation	The presence of palpable purpura.
4. Demonstrating the above criteria in small sized food vessel	Like arterioles, capillaries and precapillary venules.

Regarding immune response, uncertainty hangs as to whether vasculitis is the pathology behind cutaneous lesions of Covid 19. Such a contention would be most unwelcome from the majority dermatologist's point of view, and could even become the bone of contention, as it is almost taken for granted that the Covid 19 skin lesions are due to vasculitis. It may be noted that, it is not the considered opinion of the author but is a fall out of some reports in the literature discussed presently.

Almashat et al. [86] in their recent article exclusively devoted to the issue under consideration, the "Vasculitis in COVID-19" contend in the very opening sentence of their abstract that "Vasculitis has been linked to COVID-19 as a suspected pathological pattern in different cases, however, it is not yet considered a major pathology." The authors cite two cross references supporting their contention.

"The pathogenesis and treatment modalities are not settled as yet [87] vasculitis could be a major pathological pattern of this disease" [88].

The same authors tabulated the possible indirect evidences to support the idea of vasculitis as the pathology behind Skin lesions of Covid. If unambiguous evidence in favour of vasculitis exists, where is the scope/ need for doubts or seeking indirect evidences, that to in a review article exclusively devoted to the topic of immediate concern. This author also observed that very few histopathological reports stand by the rigours of vasculitis diagnostic criteria as reiterated in Table 6.

Many authors assert "vasculitis as the pathological hall mark of cutaneous lesions of Covid 19", without any histopathology workup. Such empty rhetoric is a disincentive for any scientific investigation aimed at finding the truth, if any, of the controversy surrounding the issue. Despite the ongoing controversy, this author in the discussion above used the term Vasculitis "without any prejudice" and "want of any better alternative term".

The type of vasulitis also appears to be controversial. Some researchers report it as leucocytoclastic vasulitis (LCV), others suggest "lymphocytic vasculitis". Other alternatives terms mentioned in the literature include

" lymphocytic thrombophilic vasculitis"
"nonvasculitic thrombosis" etc. Thrombotic microangiopathy (TMA) is the hot favourite with many as the umpteen articles report, while others try to justify "Multi systemic inflammatory disease" as a contender. The multiplicity of types of vasculitis suggested is in itself a proof that there is a confusion of the label for vasculitis. It is impossible to cite all the references supporting different above contentions but the literature is replete with references to that extent.

2.19 Type 3 (Immune Complex Disease) Hypersensitivity as Cause of Vasculitis in Covid 19

Few people are prepared to see something different in Covid vasculitis from vasculitis in other diseases, as regarding its cause. Once it is mentally accepted that Vasculitis is the cause of the pathology, the inevitable conclusion one would arrive at is that the type 3 immune/hypersensitivity reaction is the cause. Apart from time honored notion of what immune response causes a vasculitis, evidence based explanation demonstrating the "deposits of immune complexes" in the microvasulature in COVID-19 cases, assumes paramount importance. Circulating immune complexes were excluded by meticulous laboratory workup by some researchers. The search by this author, to adduced documented evidence of immune complexes in Covid 19 cutaneous lesions also turned out to be futile. The fact that Mac complex (C5-9) and even antibody to spike glycoprotein are demonstrated to be deposited, is not a substitute for accepting the deposition of immune complexes. The only definite proof acceptable is demonstration of the same either electron microscope of and by immunofourscent (IFL) studies of the immune complexes. An article by Luca Roncati, et al. [89] is exclusively written on type 3 immune complex disease in Covid 19 cutaneous lesions.The article doesn't quote evidence of deposition of immune complexes in the microvasulature, but seeks indirect evidence to prove it.

Now the author has a simple question- if the pathology is one of immune mediated vasculitis, why clinically, No PALPABLE PURPURA IS REPORTED in any of thereports in the literature on cutaneous manifestations of Covid 19, in addition to already posed question about why immune complex deposits were not reported to be detected. In the first instance itself the the Covid pathology being due to vasculitis is not put on firm footing and on top of it how its mechanism is being accepted as due to immune

complex, without proof beyond, at this point of time ? I t is hoped ear early by this author that the ongoing research would find answers to these enigmas and the pathology of cutaneous lesions in Covid 19 is put on indisputable pedestal.

On the thrombotic pathology the author avoided discussion about the involvemengv of activation of coagulative cascade and compliment activate as well as the role of innate and adaptive responses involved in the pathology and pathogenesis which were discussed elaborately in previous article by this author, titled" Acute immune mediated lung injury in Covid 119- A Review to which the readers are requested to refer for details. Similarly the spectrum of cutaneous manifestations of Covid 19 were avoided in the present context and the readers may look into the same under part 1 of the same titled article**. (See under additional information below).

The vasculitis concept would continue to rein, and not without a reason too-, but the entity should be put on firm footing by meticulous documentation of essential histopathological changes observed ,in favour of the same.

2.20 Alternative concept is Proposed

A non-vasculitis / non-immune-complex, mediated alternative, "**two hit concept"** is proposed by this author to explain the pathogenesis of cutaneous lesions of Covid 19.

The proposed alternative hypothesis is without prejudice to the probably true immune complex mediated Vasculitis'. The essence **of this two hit concept,** is that the pathology in cutaneous lesions of Covid 19 occurs in two stages .The first stage is the inflammatory attack of the microvasculature which is conceived as vasculitis. It is immaterial if the damage is done by neutrophil, lymphocyte or monocyte. The process may stop there (as in Covid toes and exanthematous lesions other than the levidoid / necrotic lesions, the first hit) or may proceed to subsequent thrombosis of microvasculature (the second hit) as in case of the levidoid / necrotic lesions, whose course seems to run parallel to that of lung pathology of Covid 19, in ICU admitted patients. While activation of the complement or M1 macrophages could explain the first hit, additional activation of the coagulative cascade is important to unveil the second hit. The clue to why the pathology stops at first hit or proceeds to the second hit is accounted by the "cross talk" between the activated complement pathways and coagulation cascade. Hence is the greater attention paid to this aspect in this article. It remains to be established what factors initiate/perpetuate the cross talk. In nutshell, the two components, the inflammatory and thrombotic events occur in succession, not invariably. This two hit concept could rationalize the treatment appropriate to the stage of the disease. Thus anti-inflammatory nature of systemic steroids make them the first choice at stage one and use of antiplatelet/anti coagulant are indicated in the second stage. It is thus staging (as first or second hit) of the disease has bearing on rational treatment. It also behoves one to monitor closely the inflammatory and coagulative profiles of a case under consideration. The patient should be closely watched for proceeding to the D I C stage, if at all, by monitoring the lab parameters for the diagnosis of the same.

2.21 The Mechanism by which the Non Immune, Non Immune Complex Hypothesis Works

The deposition of MAC complex as a procoagulant is the current thinking that is linked to the microthrombus formation in the microvasculature. The physiological purpose of MAC complex is, to destroy the virus infected host cell by way of apoptosis. Under physiological conditions a number of complement activation inhibitors guard against the destruction of the healthy host cell by generation of MAC complex. It is clear hence that the finding of MAC complex is indicative of a pathological state caused by the infected virus in the endothelial cell which suffers apoptosis subsequently. Scavenger cells, the macrophages, are called into action to clear the debris created by apoptotic cells. The macrophages have receptors for MAC as well as for the glycoprotein (leptin) antibodies- the lectin receptors. The polymorphism of macrophages is well established as well as the fact that there are M1 and M2 types of macrophages elicit inflammatory and anti-inflammatory response respectively. The M A C complex, (which stimulate the MAC receptors on the macrophages) together with Th1 cells which stimulate the M1 macrophage, release inflammatory mediators(see the "Macrophage polymorphism " for the overall role played bhM1 and M2 macrophages) which may set up the inflammation in the microvasculature . Thus a vasulitis-like inflammation independent of immune complex deposition, is possible. This

incidentally explains the first hit as referred to above. The role of TF (tissue facto) via the extrensic pathway in activating the coagulation cascade is well known in the context of Covid 19 pathology. The TF may be released by the Cytotoxic effect of NK cells of innate immune system or due to T8 cytotoxiic cells of the adaptive immune system exposing the SMC (sub mucosal muscle cells) in which T F is in abundance. Incidentally this offers an alternative explanation for the induction of the second hit. The role of Contact cascade and the protein S - protein C pathway's roles are complimentary to the in modulating the first and second hits. Also it is possible that antibody dependent complement activation with resulting in inflammatory cytokine release that leads to a hyper coagulative state, paving the way for the coagulative cascade to complete the reset of the pathology. The antibody could be one of natural antibodies of the innate immune system or the antibody to glycoprotein component of the SARS CoV 2 which is demonstrated to be deposited in the microvasulature of the skin. In this contest the observation that “detection of the anti glycoprotein antibody is associated with greater seriousness of the disease.

This alternative mechanism is suggested incase the vasculitis concept as well as the immune complex deposition theory don't stand the regours of close scrutiny on further research.

3. CONCLUSION

The pathology and pathogenesis of cutaneous manifestations of Covid 19 are reviewed. Some Contensuous issues concerning the vasculitis being the pathologic hall mark of the cutaneous lesions of Covid 19 as well as immune complex mediation of the vasculitis are pointed out. An alternative non- immune non- vasculitis mechanism to explain the pathogenesis is suggested on the basis of the proposed two hit hypothesis. Though, it appears to be the favored term to explain both the systemic and local manifestations of Covid 19, TMA fails to explain the vasulitis component of the pathology and this lacuna, needs to be circumvented , should the rightful place of TMA is to be retained. TMA does not explain the acral and more benign exanthematous manifestations. In view of the above considerations, this author suggests “**lymphocytic vasculitis"** as a better term for both the local acral lesions (Covid toes) and the already referred more benign exanthematous lesions seen in Covid 19. For the levidoid /necrotic lesions with the concurrent systemic pathology often seen, as In lungs of Covid 19, the term “**Lymphocytic thrombophilic vasculitis** is suggested. This term has the advantage of covering both the inflammatory and thrombotic events. More so, it reflects the uniformly observed” perivascular lymphocytosis histologically and uncompromisingly retains the label of vasculitis the necessity for focussed future research on the pathology and pathogenesis is stressed.

The Author's Articles to which Reference is Made in the Text

*Prasad, A. S. V. (2020). Acute Immune Mediated Lung Injury in COVID 19: A Review. Asian Journal of Immunology, 4(2), 11-30.
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CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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