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Correlation between Systemic lupus erythematosus and CD 163

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Abstract: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the breaking of tolerance to nuclear self-antigens and the production of autoantibodies. This complex and challenging disease can involve several organs in the body such as the joints, skin, kidney, eyes, heart, and muscles. CD163 is a 130 kDa protein .It is a transmembrane scavenger receptor for hemoglobin-haptoglobin complexes and is expressed exclusively on macrophages and monocytes. It contributes to the prevention of oxidative stress and inflammation associated with extracellular metabolism of hemoglobin. In addition to the membrane CD163, a soluble form of CD163 (sCD163), which is produced by shedding of CD163, is present in blood and various tissue fluids. The major function of M2 macrophages is resolution of inflammation, tissue remodeling, and promotion of fibrosis. The chief anti-inflammatory cytokines secreted by them are IL-10, arginase-1, and transforming growth factor–β. M2 macrophages have been thought to play key pathogenic role in development of various autoimmune diseases including SLE. Since these macrophages express CD163 which can be proteolytically cleaved from the surface and released in the circulation as a soluble protein, soluble CD163 (sCD163) may correlate with disease activity. sCD163 may participate in the immunopathological process of lupus nephritis(LN) as an inflammatory mediator. Serum sCD163 levels correlate with the severity of LN and are an important indicator of poor renal prognosis in patients with LN, suggesting that macrophage activation is involved in the development of LN. Serum sCD163 shows potential as an effective biological marker for LN diagnosis, differential diagnosis and prognosis evaluation.

Keywords: *Systemic lupus erythematosus, Cluster of Differentiation 163*

Introduction.

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the breaking of tolerance to nuclear self-antigens and the production of autoantibodies [1]. This complex and challenging disease can involve several organs in the body such as the joints, skin, kidney, eyes, heart, and muscles [1].

The incidence and prevalence of SLE vary widely in population demographics, socioeconomic factors, and certain ethnic populations, such as Hispanic, Black, and Asian populations. SLE may be more prevalent among most ethnic groups in low- and middle-income countries. The SLE incidence varied from 0.3–8.7 per 100,000 persons [2].

Although the etiology of the disease is not completely understood, several environmental triggers, along with genetic factors, are thought to contribute to the pathogenesis of the disease [3].

SLE is characterized by the production of abundant autoantibodies, deposition of massive immune complexes, upregulation of inflammatory and immune responses, and damage to different tissues. Great gains have been made in understanding SLE through the use of genetic variant identification, mouse models, gene expression studies, and epigenetic analyses. Collectively, these studies support the concept that defective clearance of immune complexes and biological waste (such as apoptotic cells), neutrophil extracellular traps, nucleic acid sensing, lymphocyte signaling, and interferon production pathways are all central to loss of tolerance and tissue damage [4].

Disruption of immune tolerance and sustained generation of autoantibodies against nuclear autoantigens are two major hallmarks of SLE. Apoptosis and other programmed cell death pathways have been defined and intensively investigated, including NETosis, necroptosis, pyroptosis, and autophagy. Dysregulated cell death in combination with defective clearance of dying cells has been suggested to contribute to the release of damage-associated molecular patterns (DAMPs), amplification of inflammatory and immune responses, production and release of autoantigens, and tissue damage in SLE [5].

Diagnosis and Disease Activity and Severity Measurement:

1. Diagnostic Criteria:

The Systemic Lupus International Collaborating Clinics (SLICC) classification criteria was introduced in 2012 [Table 1]. To be classified as SLE, the patient must meet at least 4 of 17 criteria, including at least 1 clinical and 1 immunological criterion or documented lupus nephritis (LN) with antinuclear antibodies (ANA) and/or anti-dsDNA. SLICC criteria is reported to have partially succeeded in improved performance over the ACR criteria, in that it had increased sensitivity (92–99% vs 77–91%) at the expense of reduced specificity (74–88% vs 91–96%) [6].

Table (1): SLICC classification critetia

Clinical Criteria
1. Acute or subacute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral/Nasal ulcers
4. Non scarring alopecia
5. Inflammatory synovitis with physician-observed swelling of two or more joints OR tender joints with morning stiffness
6. Serositis
7. Renal: 24 hr urine protein representing at least 500 mg of protein/24 hr or red blood cell casts
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)
9. Hemolytic anemia
10. Leukopenia (< 4000/ mm^3 at least once) OR Lymphopenia (<1000/ mm^3 at least once).
11.Thrombocytopenia (<100,000/ mm^3) at least one.
Immunologic Criteria

1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)
3. Anti-Sm.
4. Antiphospholipid antibody: . Positive test for lupus anticoagulant. . Anticardiolipin antibody eg: igG,igM and igA (medium or high titer). . Positive test for anti-B2 glycoprotein 1.
5.Low complement: low C3, low C4, low CH50.
6. Direct Coombs test in absence of hemolytic anemia.

(Petri et al. ,2012).

A novel SLE classification criteria jointly supported by the European League Against Rheumatism (EULAR) and ACR was introduced in 2019 [Table 2], based on two concepts, namely the presence of ANA as an entry criterion coupled with a scoring system based on variably weighed clinical and laboratory features. Performance characteristics in adult-onset SLE found the EULAR/ACR to have sensitivity similar to the SLICC criteria (98% vs 95% for SLICC and 85% for ACR 1997) while maintaining the specificity of the ACR 1997 criteria (97% vs 95% for ACR 1997 and 90% for SLICC) [7].

Table(2): The 2019 EULAR/ACR classification criteria for SLE

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)	
If absent, do not classify as SLE If present, apply additive criteria	
-Do not count a criterion if there is a more likely explanation than SLE. -Occurrence of a criterion on at least one occasion is sufficient. -SLE classification requires at least one clinical criterion and ≥10 points. -Criteria need not occur simultaneously. -Within each domain, only the highest weighted criterion is counted toward the total scores:	
Clinical domains and criteria	***Weight***
Constitutional **Fever**	 **2**
Hematologic **Leukopenia** **Thrombocytopenia** **Autoimmune hemolysis**	 3 4 4
Neuropsychiatric **Delirium** **Psychosis** **Seizure**	 2 3 5
Mucocutaneous **Non scarring alopecia** **Oral ulcers**	 **2** **2**

Subacute cutaneous OR discoid lupus **Acute cutaneous lupus**	**4** **6**
Serosal **Pleural or pericardial effusion** **Acute pericarditis**	 **5** **6**
Musculoskeletal **Joint involvement**	 **6**
Renal **Proteinuria >0.5g/24h** **Renal biopsy Class II or V lupus nephritis** **Renal biopsy Class III or IV lupus nephritis** ***Immunology domains and criteria***	 **4** **8** **10**
Antiphospholipid antibodies **Anti-cardiolipin antibodies OR** **Anti-β2GP1 antibodies OR** **Lupus anticoagulant**	 **2**
Complement proteins **Low C3 OR low C4** **Low C3 and low C4**	 **3** **4**
SLE-specific antibodies **Anti-dsDNA antibody* OR** **Anti-Smith antibody**	 **6**

NB: Classify as Systemic Lupus Erythematosus when score is 10 or more if entry criterion fulfilled.

(Aringer et al., 2019).

2. Disease Activity:

For the determination of disease activity in SLE, various scoring systems have been developed, including the Systemic Lupus Activity Measure (SLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Lupus Activity Index (LAI), British Isles Lupus Assessment Group index (BILAG), and the European Consensus Lupus Activity Measure (ECLAM) that mainly include clinical findings and laboratory parameters [8].

SLE Disease Activity Score (SLEDAI-2K):

SLEDAI-2K is based on the presence of 24 descriptors in nine organ systems over the preceding 30 days. Descriptors of SLEDAI-2K are documented as present or absent. Each of the descriptors has a weighted score and the total score of SLEDAI-2K is the sum of all 24 descriptor scores. The total SLEDAI-2K score falls between 0 and 105, with higher scores representing higher disease activity [Figure 1] [9].

SLEDAI-2K (30 DAYS)
DATA COLLECTION SHEET

Study No.:_____ Patient Name:_____ Visit Date: _____ _____ _____
d m yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 30 days)

Weight	SCORE	Descriptor	Definition
8	☐	Seizure	Recent onset, exclude metabolic, infections, or drug causes.
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	☐	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	☐	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	☐	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	☐	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exlcude arteriosclerosis.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	Arthritis	≥2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary casts	Heme-granular or red blood cell casts.
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other cause.
4	☐	Proteinuria	>0.5 gram/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	Rash	Inflammatory type rash.
2	☐	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	☐	Mucosal ulcers	Oral or nasal ulcerations.
2	☐	Pleurisy	Pleuritic chest pain with pleural rub or effusion or pleural thickening.
2	☐	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	☐	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	☐	Fever	>38° C. Exclude infectious cause.
1	☐	Thrombocytopenia	<100,000 platelets/× 10^9/L, exclude drug causes.
1	☐	Leukopenia	<3000 white blood cells/× 10^9/L, exclude drug causes.

3. Disease Severity Measurement:

The damage should be assessed annually using the SLICC/ACR Damage Index for SLE (Systemic Lupus International Collaborating Clinics/American College of Rheumatology) [10].

Item	Score
Ocular (either eye by clinical assessment)	
Any cataract ever	0, 1
Retinal change or optic atrophy	0, 1
Neuropsychiatric	
Cognitive impairment (eg, memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) **or** major psychosis	0, 1
Seizures requiring therapy for 6 months	0, 1
Cerebrovascular accident ever (score 2 if >1)	0, 1, 2
Cranial or peripheral neuropathy (excluding optic)	0, 1
Transverse myelitis	0, 1
Renal	
Estimated or measured glomerular filtration rate <50%	0, 1
Proteinuria >3.5 g/24 h	0, 1
or end-stage renal disease (regardless of dialysis or transplantation)	**or** 3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	0, 1
Pulmonary fibrosis (physical and radiographical)	0, 1
Shrinking lung (radiograph)	0, 1
Pleural fibrosis (radiograph)	0, 1
Pulmonary infarction (radiograph)	0, 1
Cardiovascular	
Angina **or** coronary artery bypass	0, 1
Myocardial infarction ever (score 2 if >1)	0, 1, 2
Cardiomyopathy (ventricular dysfunction)	0, 1
Valvular disease (diastolic murmur, or systolic murmur >3/6)	0, 1
Pericarditis for 6 months **or** pericardiectomy	0, 1

Item	Score
Peripheral vascular	
Claudication for 6 months	0, 1
Minor tissue loss (pulp space)	0, 1
Significant tissue loss ever (eg, loss of digit or limb) (score 2 if >1 site)	0, 1, 2
Venous thrombosis with swelling, ulceration **or** venous stasis	0, 1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if >1 site)	0, 1, 2
Mesenteric insufficiency	0, 1
Chronic peritonitis	0, 1
Stricture **or** upper gastrointestinal tract surgery ever	0, 1
Chronic pancreatitis	0, 1
Musculoskeletal	
Muscle atrophy or weakness	0, 1
Deforming or erosive arthritis (including reversible deformities, excluding avascular necrosis)	0, 1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0, 1
Avascular necrosis (score 2 if >1)	0, 1, 2
Osteomyelitis	0, 1
Tendon rupture	0, 1
Skin	
Scarring chronic alopecia	0, 1
Extensive scarring of panniculum other than scalp and pulp space	0, 1
Skin ulceration (excluding thrombosis for >6 months)	0, 1
Premature gonadal failure	0, 1
Diabetes (regardless of treatment)	0, 1
Malignancy (exclude dysplasia) (score 2 if >1 site)	0, 1

Cluster of Differentiation 163 (CD163)

CD163 is a 130 kDa protein. It is a transmembrane scavenger receptor for hemoglobin-haptoglobin complexes and is expressed exclusively on macrophages and monocytes. It contributes to the prevention of oxidative stress and inflammation associated with extracellular metabolism of hemoglobin. In addition to the membrane CD163, a soluble form of CD163 (sCD163), which is produced by shedding of CD163, is present in blood and various tissue fluids [11].

The main function of CD163 is to remove hemoglobin-haptoglobin complexes from the blood circulation during intravascular hemolysis. CD163 is composed of a short intracellular domain, a single transmembrane segment, and an extracellular domain consisting of nine scavenger receptor cytokine-rich (SRCR) receptor class B

domains [Figure 2]. Different isoforms of CD163 have been identified, including three splice variants in which the cytoplasmic tail differs in length. While the CD163 short tail isoform is the most abundant, all variants display endocytic activity [12].

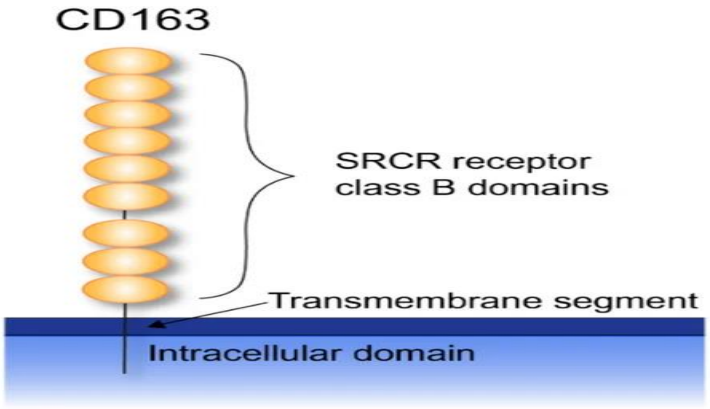

Figure 1: CD163 structure [12].

The innate immune system plays a major role in both the activation and regulation of the immune response. Innate immune cells that mediate immune regulation include gamma–delta T cells, innate lymphoid cells (ILCs), and M2 macrophages. Among these, the role of M2 macrophages is currently being explored in the pathogenesis of various rheumatic diseases including SLE, spondyloarthropathy, macrophage activation syndrome (MAS), IgG4-mediated diseases, and systemic sclerosis [13].

Macrophages can be polarized from a classically activated M1 state to an alternatively activated M2 subset, and vice versa under different conditions. Pathogen-clearing M1 produce pro-inflammatory cytokines in response to lipopolysaccharide and other inflammatory triggers. On the other hand, resolving M2 are the mononuclear phagocytes that could engulf apoptotic cells in the early stages of apoptosis in an anti-inflammatory manner. This is associated with an increase in the production of anti-inflammatory and decreasing pro-inflammatory cytokines [14].

M2 macrophages can be further classified as M2a, M2b, and M2c, which display distinct functions of pro-fibrosis, immunity-regulation, and remodeling or anti-inflammation, respectively. CD163 has been recognized as a marker of M2 macrophages, especially M2c. Therefore, CD163 has an anti-inflammatory function [15].

Oxidative stress or inflammatory stimuli can release sCD163 from the cell surface through proteolytic cleavage. Moreover, sCD163 is found to be increased during wound healing, giving a possible role of CD163 in the pathogenesis of fibrotic diseases and the remodeling of connective tissues. CD163 is found to be increased in many chronic inflammatory conditions and is supposed to have a potential anti-inflammatory function. CD163-expressing macrophages can take up haptoglobin-hemoglobin complexes, leading to the increased secretion of IL-10 and the expression of hemeoxygenase −1 [16].

Additionally, CD163 has also been reported to bind and degrade the inflammatory cytokine tumor necrosis factor-like weak inducer of apoptosis (TWEAK) as well as to recognize and mediate a local immune response to bacteria and internalize virus. CD163 is often used as an M2 marker although it seems apparent that only a subpopulation of M2s are CD163+, so in essence, a distinct CD163+ subpopulation may be defined [17].

While CD163+ macrophages can only be observed and analyzed on tissue biopsies, soluble CD163 (sCD163), derived from the extracellular portion of CD163 when cleaved by metalloproteinases, can easily be measured in diverse body fluids, including serum, urine, synovial fluid, and cerebrospinal fluid. The shedding of CD163 is enhanced by various pathological conditions including infections, liver diseases, malignancies, and autoimmune diseases. Indeed, sCD163 has been used as a biomarker for macrophage activation in several inflammatory diseases [18].

CD163 and Lupus Nephritis

The major function of M2 macrophages is the resolution of inflammation, tissue remodeling, and promotion of fibrosis. The chief anti-inflammatory cytokines secreted by them are IL-10, arginase-1, and transforming growth factor–β. M2 macrophages have been thought to play a key pathogenic role in the development of various autoimmune diseases including SLE. Since these macrophages express CD163 which can be proteolytically cleaved from the surface and released in the circulation as a soluble protein, soluble CD163 (sCD163) may correlate with disease activity. [19].

sCD163 may participate in the immunopathological process of lupus nephritis (LN) as an inflammatory mediator. Serum sCD163 levels correlate with the severity of LN and are an important indicator of poor renal prognosis in patients with LN, suggesting that macrophage activation is involved in the development of LN. Serum sCD163 shows potential as an effective biological marker for LN diagnosis, differential diagnosis, and prognosis evaluation [20].

In LN patients, CD163 cells have been found in cellular crescents, proliferative glomerular, and acute tubulointerstitial lesions. CD163 gene expression is increased in glomeruli from patients with active LN compared with healthy kidney donors. This has been confirmed by a study revealing M2c macrophages expressing the CD163 receptor infiltrate kidney tissue and represent the most abundant cells detected in urine from LN patients. [21].

Renal biopsy findings on LN patients that showed infiltration of CD163+ macrophages in tubulointerstitial and glomerular lesions supports their pathogenic role [22].

CD163 and RA

Functionally, patients with early RA had significantly higher plasma levels of sCD163 than after 9 months of treatment; these levels are associated with disease activity and predict radiographic progression. Conversely, plasma sCD163 levels decreased significantly after 3 months of treatment from the OPERA (optimized treatment algorithm in early rheumatoid arthritis) trial, which correlated with the investigated disease activity markers. More importantly, sCD163 could be observed not only in plasma but also in other body fluids such as cerebrospinal fluid (CSF) and synovial fluid (SF) [23].

CD163 and Stills Disease

Soluble CD163 was evaluated in patients with adult-onset Still's disease (AOSD). Even if not highly specific for the disease, sCD163 was significantly increased in active patients, representing a possible marker for disease activity. Moreover, in patients with AOSD, the sCD163 serum levels were found to positively correlate with ferritin serum levels suggesting a possible role for macrophages in ferritin production. So, sCD163 is identified as a marker of disease activity in adult-onset Still's disease, which is found to be correlated with ferritin expression in both the lymph node and tonsil [24].

CD163 and Systemic Sclerosis (SSc)

Systemic sclerosis (SSc) patients with elevated serum sCD163 levels tend to develop pulmonary hypertension. SSc patients with elevated serum sCD163 levels, disease duration was significantly shorter, suggesting that these patients may have severe symptoms. Furthermore, the right ventricular systolic pressure (RVSP) value was significantly higher, and diffuse capacity of the lungs for carbon monoxide (%DLco) was significantly lower in patients with higher sCD163 levels than those with normal levels. Both the higher RVSP and lower %DLco value in patients with elevated serum sCD163 levels may predict the development of pulmonary hypertension in these patients. So, it's suggested that serum sCD163 levels are useful for diagnosis and can be a marker of pulmonary hypertension in patients with SSc [16].

CD163 and Glomerulonephritis

In addition, the number and frequency of CD163-positive cells (M2 macrophages) tend to increase in acute post-streptococcal glomerulonephritis, suggesting that the severity of endothelial injury might be related to the difference in the phenotypes of infiltrating inflammatory cells [25].

CD163 and Polymyositis

Serum soluble CD163 (sCD163) levels, mainly secreted by monocyte/macrophage lineage, were significantly increased in the patients with polymyositis (PM) and dermatomyositis (DM) compared with healthy controls.

The involvement of CD163+ macrophage infiltration in the muscle is highlighted in the development of PM/DM [26].

CD163 and Kawazaki Disease (KD)

Moreover, Serum levels of sCD163, a macrophage activation marker, are elevated in patients with acute-phase (KD). After initial intravenous immunoglobulin (IVIG), sCD163 was increased in initial IVIG-responders but not in non-responders. Close correlation of serum sCD163 with ALT and AST suggest that liver function abnormality commonly seen in KD may be a result of macrophage activation. Among the initial IVIG non-responders, sCD163 was higher in patients who responded to the additional IVIG [27].

CD163 and Spondyloarthropathy (SpA)

In keeping with the local production of sCD163 in SF, an increased proportion of CD163+ macrophages and decreased CD69+ lymphocyte numbers were observed in SpA synovium, which reflected the dual involvement of CD163+ macrophages in both SpA synovitis with global inflammation and impairment of T cell activation [28].

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