Renal Involvement in Patients with Vasculitis: Update in Diagnosis and Management

Essay

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By

Walaa Attia El Sayed Sheba
M.B.B.ch.
Faculty of Medicine - Alexandria University

Under Supervision of

Prof. / Dahlia Abdel-Mohsen Hussein
Professor of Internal Medicine & Rheumatology
Faculty of medicine - Ain Shams University

Dr. / Hanan Mohammed Farouk
Assistant Professor of Internal Medicine & Rheumatology
Faculty of medicine - Ain Shams University

Dr. / Sameh Abdel-Moteleb Hassan
Lecturer of Internal Medicine & Rheumatology
Faculty of medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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تأثر الكلى فى مرض التهاب الاوعية الدموية:

التشخيص والجديد فى العلاج

بحث مقدم لكليه الطب جامعة عين شمس إيفاءا جزئيا لشروط الحصول
على درجه الماجستير فى الأمراض الباطنة

مقـــــدم من

ولاء عطيه السيد شيبه

بكالوريوس الطب والجراحة
كلية الطب - جامعة الأسكندريه

المشرفون

الأستاذ الدكتور/داليا عبد المحسن حسين
أستاذ الأمراض الباطنة والأمراض الروماتيزمية
كلية الطب - جامعة عين شمس

دكتور/حنان محمد فاروق
أستاذ مساعد الأمراض الباطنة والأمراض الروماتيزمية
كلية الطب - جامعة عين شمس

دكتور/سامح عبد المطلب حسن
مدرس الباطنة العامة والأمراض الروماتيزمية
كلية الطب - جامعة عين شمس

كلية الطب- جامعة عين شمس

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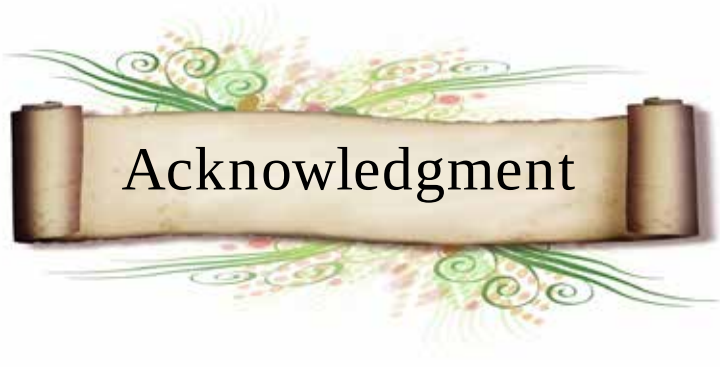

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﴿رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي أَنْعَمْتَ
عَلَيَّ وَعَلَى وَالِدَيَّ وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ
وَأَصْلِحْ لِي فِي ذُرِّيَّتِي إِنِّي تُبْتُ إِلَيْكَ وَإِنِّي
مِنَ الْمُسْلِمِينَ﴾

صدق الله العظيم

سورة الأحقاف الآية (١٥)

List of Abbreviations	
AAVs	ANCA associated vasculitis
ABAVAS	Randomized trial of Abatacept for systemic vasculitis
Abs	Antibodies
ACR	American College of Rheumatology
ANA	Antinuclear Antibody
ANCA	Antineutrophil cytoplasmic antibodies
Anti-GBM	Anti-glomerular basement membrane antibodies
APRIL	A proliferation –inducing ligand
ASVV	ANCA associated small vessel vasculitis
ATG	Antimocyte globulin
ATN	Acute tubular necrosis
BLYS	B-lymphocyte simulater
BVAS	Birmingham Vasculitis Activity Score
C3	Complement 3
C4	Complement 4
C5	Complement 5
C-ANCA	Cytoplasmic antineutrophil cytoplasmic antibody
CD 4	Cluster Differentiation 4
CD20	Cluster Differentiation 20
CD 28	Cluster Differentiation 28
CD 52	Cluster Differentiation 52
CSS	Churg Strauss Syndrome
CYCAZAREM	Prospective randomized control trial of Cyclophosphamide and azathioprine remission
CYCLOPS	Trial of pulsed versus oral cyclophosphamide
DAH	Diffuse alveolar hemorrhage
DHFR	Dihydrofolate reductase
ELISA	Enzyme linked immunosorbent assay
ESR	Erythrocyte sedimentation rate

EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Study Group
FH2	Dihydrofolic acid
Fc	Crystalline fragment
GCA	Giant cell arteritis
GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHV	Human Herpes virus
HIV	Human immundeficiency virus
HLA	Human leucocyte antigen
HSP	Henoch-Schölein Purpura
IFN-gama	Interferon-gama
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMPROVE trial	Mycophenolate mofetil versus azathioprine trial
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
LTMAs	Leukotriene modifying agents
MAINRITSAN	MAINtenance of remission using RITuximab in Systemic ANCA associated vasculitis trial
MCP1	Monocyte chemoattractant protein 1
MGCs	Multinucleated giant cells
MPGN	Membranoproliferative glomerulonephritis
MMF	Mycophenolate mefetil
MMP2	Matrix metalloproteinases
MPA	Microscopic polyangitis
MPO	Myloperoxidase
MTX	Methotrexate
MYCYC	Mycophenolate and cyclophosphamide trial

NIH	National Institute of Health
NPV	Negative predictive value
PAN	Polyarteritis nodosa
p-ANCA	Perinuclear antineutrophil cytoplasmic antibody
PCP	Pneumocystis carinii pneuomonia
PDGF	Platelet derived growth factor
PE	Plasma exchange
PMR	Polymyalgia rheumatic
PPV	Positive predictive value
PR3	Proteinase 3
PSS	Primary Systemic Sclerosis
RA	Rheumatiod arthritis
RCT	Randomized controlled trial
RF	Rheumatoid factor
RITUXVAS	Randomized trial of Rituximab versus cyclophosphamide for renal vasculitis
RPGN	Rapidly progressive glomerulonephritis
SLE	Systemic Lupus Erythematosus
S cr	Serum creatinine
SS	Sjogren's syndrome
SYK	Spleen tyrosine kinase
TACI	Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TGF-beta	Transforming growth factor-beta
Th 17	T- helper 17 cells
TIMP	Tissue inhibitor of MMP
TNF-α	Tumor necrosis factor-alpha
TTP	Thrombotic thrombocytopenic purpura
UCTD	Unclassified Connective Tissue Disease
VEGF	Vascular endothelial growth factor
WBC	White blood cell count
WG	Wegener's granulomatosis

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INTRODUCTION

Vasculitis is inflammation of blood vessels with demonstrable structural injury of the vessel wall. The clinical and pathological features are variable and depend on the type and the size of the involved blood vessels and the tissue and organ damage caused by vascular occlusion **(*Saleh and John, 2005*).**

The main types of vasculitides can be described using clinical features and pathological findings according to the Chapel Hill Classification (1994) into: Large vessel vasculitis (Giant Cell arteritis,Takayasu's arteritis) Medium vessel vasculitis (Polyarteritis Nodosa, Kawasaki's disease) Small vessel vasculitis (ANCA associated including Wegener's granulomatosis, Churg Strauss syndrome, Microscopic polyangitis and ANCA unassotiated including Henoch-Schönlein purpura, Essential cryoglobulinemic vasculitis and cutaneous leukocytoclastic angitis) **(*Saleh and John, 2005*).**

Vasculitides affecting the kidneys are typically associated with hematuria and proteinuria, frequently presenting as a rapidly progressive necrotizing glomerulonephritis (Pauci-immune necrotizing glomerulonephritis). Glomerular injury occurs in the setting of the small vessel vasculitis, associated with antineutrophil cytoplasmic autoantibodies (ANCA), antiglomerular basement membrane antibodies (anti-GBM), or the presence of immune complex formation such as with Henoch-Schönlein Purpura (HSP), cryoglobulinemic vasculitis, and systemic lupus erythematosus (SLE) ***(Walters et al., 2010).***

Pauci-immune necrotizing glomerulonephritis is a somewhat confusing term. Pauci originates from the Latin word paucus meaning little or few. It reflects the almost complete absence of immunoglobulin deposits (as assessed by immunofluorescence) when studying renal biopsies of a subgroup of patients with rapidly progressive glomerulonephritis ***(Rutgers et al., 2010).***

Historically, pauci-immune glomerulonephritis has been described as a form of glomerulonephritis with no evidence of linear immunoglobulin deposition (type I glomerulonephritis, as in Goodpasture disease) or immune complex deposition (type II glomerulonephritis, as in lupus nephritis). However, paucity of immune deposits does not imply that the immune system is not involved in the disease process; on the contrary, pauci-immune renal disease is believed to be a typical immune-mediated disease and is treated accordingly ***(Jabur and Saeed, 2010).***

Why is the disease sometimes limited to the kidneys?

This issue has no definite answer. Two types of reasoning exist. First, the disease process itself might specifically target a particular, organ-specific vasculature. Second, the unique characteristics of certain types of vasculature could make them vulnerable to an immunologically mediated attack ***(Flint et al., 2010).***

The unique characteristics could be intrinsically present but not previously recognized by the immune system (eg, the noncollagenous domain of type IV collagen in Goodpasture disease), or could be acquired

by the vasculature either by deposition of antigen (eg, in situ formation of immune complexes in poststreptococcal glomerulonephritis), change of a preexisting antigen (formation of neoepitopes), or change in endothelial function ***(Ball, 2010).***

Essential to the pathogenesis of pauci-immune renal disease is inflammation of blood vessels. The endothelium plays a crucial role in this process. Thus, organ-specific endothelial antibodies could explain organ-specific disease manifestations, although the presence of these antibodies in most patients was not confirmed ***(Bollee et al., 2009).***

The glomerulus has a unique type of fenestrated endothelium allowing for filtration of blood and the production of urine. The fenestrae are covered by a highly negatively charged glycocalyx, which is in part responsible for the glomerular filtration barrier. These characteristics could facilitate capturing of ANCA antigens (especially the highly positively charged myeloperoxidase) resulting in local inflammation in the presence of ANCA ***(Rihova, 2009).***

Also, local cytokine production in the kidney could induce on-site neutrophil priming, a necessary step for ANCA-induced neutrophil activation and endothelial damage. The unique microvasculature in the glomerulus could allow local trapping of activated neutrophils and thus could be responsible for local inflammation. Likely a combination of local and systemic factors determines the location and severity of active vasculitis and its disease course ***(Shaikh and Ansari, 2009).***

But renal involvement is more frequently part of a multiorgan disease that may affect the skin, upper and lower respiratory tracts, and the musculoskeletal, gastrointestinal, and nervous systems ***(Galesic et al., 2009).***

Renal involvement is common in any of the forms of systemic vasculitis. These include classic polyarteritis nodosa, Wegener's granulomatosis, microscopic polyarteritis, Churg-Strauss syndrome, and the hypersensitivity vasculitides (including Henoch-Schönlein purpura, mixed cryoglobulinemia, and serum sickness) ***(Walters et al., 2008).***

In Polyarteritis nodosa (PAN) the kidneys are the most commonly involved organ. Renal involvement frequently leads to variable degrees of renal insufficiency and hypertension. In addition, rupture of renal arterial aneurysms can cause perirenal hematomas. Multiple renal infarctions may also develop in those with severe vasculitis. Incomplete luminal narrowing of the inflamed arteries leads to glomerular ischemia but not inflammation or necrosis ***(Unverdi et al., 2009).***

In Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) renal biopsy reveals a segmental necrotizing glomerulonephritis with few or no immune deposits (pauci-immune) on immunofluorescence and electron microscopy. The glomerular involvement is often accompanied by mononuclear tubulointerstitial infiltrates. However, occasional patients present with an interstitial nephritis with or without granuloma formation in the absence of the typical glomerular lesions.

Such patients may subsequently develop the classic pauci-immune necrotizing glomerulonephritis ***(Chen et al., 2007).***

In The Churg-Strauss syndrome (CSS) kidney affection may be more common than is generally reported. On renal biopsy, focal segmental glomerulonephritis is the predominant lesion, and is often associated with necrotizing features and crescents ***(Keogh and Specks, 2006).***

In hypersensitivity vasculitis, the term "hypersensitivity vasculitis" refers to a vasculitis of small blood vessels of the skin (especially arterioles and venules), which is secondary to an immune response or hypersensitivity reaction to an exogenous substance. The nomenclature of hypersensitivity vasculitis is diverse and often confusing. Names often used interchangeably but inappropriately have included drug-induced vasculitis, leukocytoclastic vasculitis, cutaneous vasculitis, serum sickness or serum sickness-like reactions and allergic vasculitis. Serum sickness and serum sickness-like reactions may, but in many cases do not, have a vasculitic component. Renal involvement is usually mild ***(Jennett and Falk, 2004).***

Vasculitis may also occur as a secondary feature in other diseases, such as (infection related vasculitis as HCV infection, connective tissue disease as RA &SLE, malignancy related vasculitis as lymphoma & leukemia, drug hypersensitivity related vasculitis and post organ transplant vasculitis) ***(Luqmanic and Pathare , 2005).***