

Tropical diseases-associated kidney injury*

Lesão renal associada a doenças tropicais

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SUMMARY

BACKGROUND AND OBJECTIVES: Infectious and parasitic diseases are important morbidity factors and mortality causes, accounting for more than 13 million deaths a year - one in two deaths in developing countries. Despite health providing expansion throughout, large populations are still at risk in many areas of Asia, Middle East, Africa and Americas. Tuberculosis, specially, poses new challenges, as nearly two billion people may have latent disease. Malaria kills over one million people a year - most of them young children. Most malaria deaths occur in Africa, where it accounts for one in five of all childhood deaths - women are especially vulnerable during pregnancy. Many of these illnesses may be accompanied by acute or chronic kidney involvement.

CONTENTS: Acute kidney injury (AKI) and tubulointerstitial defects are frequently observed in the course of leptospirosis, malaria, and the several viral hemorrhagic fevers. All known varieties of glomerular lesions have been observed, with clinical presentations ranging from mild proteinuria or hematuria, to nephrotic syndrome. Tubular dysfunction may also occur, particularly in visceral leishmaniasis and leprosy, where distal tubular acidosis may be an early clinical expression of the disease.

CONCLUSION: To summarize, almost every known infectious and parasitic disease may present with kidney involvement, varying from mild to extreme, and additionally burdening usually overwhelmed health services.

Keywords: Infectious and parasitic diseases, Leprosy, Leptospirosis, Malaria, Schistosomiasis, Systemic histoplasmosis, Tuberculosis, Visceral leishmaniasis.

RESUMO

JUSTIFICATIVA E OBJETIVOS: As doenças infecciosas e parasitárias são fatores importantes de morbidade e causas de mortalidade, sendo responsáveis por mais de 13 milhões de mortes por ano - uma em cada duas mortes em países em desenvolvimento. Apesar da expansão do atendimento de saúde em todos os locais, grandes populações ainda estão em risco em muitas áreas da Ásia, Oriente Médio, África e Américas. A tuberculose, em especial, apresenta novos desafios, já que quase dois bilhões de pessoas podem ter uma doença latente. A malária mata mais de um milhão de pessoas por ano - a maioria delas crianças. A maioria das mortes por malária ocorre na África, onde é responsável por uma em cada cinco mortes de crianças - as mulheres são especialmente vulneráveis durante a gravidez. Muitas destas doenças podem ser acompanhadas por acometimento renal agudo ou crônico.

CONTEÚDO: A lesão renal aguda (LRA) e os defeitos túbulo-intersticiais são frequentemente observados no curso de leptospirose, malária, e de várias febres hemorrágicas virais. Todas as variedades conhecidas de lesões glomerulares foram observadas, com apresentações clínicas que variam de ligeira proteinúria ou hematuria até síndrome nefrótica. Também pode ocorrer disfunção tubular, especialmente na leishmaniose visceral e na lepra, onde a acidose tubular distal pode ser uma manifestação clínica precoce da doença.

CONCLUSÃO: Em resumo, quase todas as doenças infecciosas e parasitárias conhecidas podem apresentar comprometimento renal, variando de leve a extremo e, sobrecarregando ainda mais os serviços de saúde geralmente já sobrecarregados.

Descritores: Doenças infecciosas e parasitárias, Esquistossomose, Histoplasmosse sistêmica, Leishmaniose visceral, Lepra, Leptospirose, Malária, Tuberculose.

INTRODUCTION

Acute kidney injury (AKI) and tubulointerstitial defects are frequently observed in the course of tropical diseases, such as leptospirosis, malaria, and viral hemorrhagic fevers^{1,2}. All known varieties of glomerular lesions have been observed, with clinical presentations ranging from mild proteinuria or hematuria, to nephrotic syndrome³. Tubular dysfunction may also occur, particularly in visceral leishmaniasis and leprosy, where distal tubular acidosis may be an early clinical expression of the disease^{4,5}. The present article reviews the clinical aspects of tropical diseases-associated kidney diseases.

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TUBERCULOSIS

Introduction

Tuberculosis is a systemic disease caused by the *Mycobacterium tuberculosis*, which is highly prevalent in some poor areas of the world. Extrapulmonary TB became more common with the advent of infection with human immunodeficiency virus, and by the increase in the number of organ transplantations, which also lead to immunosuppression of thousand of persons⁶.

Clinical presentation

The most prevalent clinical presentation is pulmonary cavitations, usually accompanied by productive cough, fever, night sweating, and wasting. However, following a primary respiratory inoculation, widespread seeding of bacilli may occur and typical lesions may develop in other locations, such as the pleural cavity, lymphatic nodes, and eventually the urogenital tract⁷.

Urogenital tuberculosis

The spectrum of urogenital tuberculosis includes the classical renal tuberculosis, interstitial nephritis, glomerular disease (including proliferative glomerulonephritis), end-stage renal disease, dialysis and transplantation-associated tuberculosis and genital tuberculosis (most commonly affecting the epididymus and prostate)^{6,8}.

This is a frequent extra-pulmonary location for *Mycobacterium tuberculosis* lesions⁷. Typically the lesions initiate at the kidneys, spreading distally to the ureters, bladder and testicles. Early granulomatous kidney disease may present as proteinuria, pyuria, and loss of kidney function. Lower urinary symptoms occur whenever the disease spreads down to the ureters and bladder. Urinary symptoms suggestive of urinary infection, accompanied by pyuria and hematuria with no bacterial growth, point to urogenital tuberculosis. Advanced disease may cause obstructive uropathy, bladder defects, and loss of kidney function^{6,9}.

Images

Ultrasonography, computerized tomography and magnetic nuclear resonance will demonstrate grossly distorted ureters, with alternating stenotic and dilated areas, reduced bladder volume, hydronephrosis, and reduced kidneys in advanced disease^{6,9,10}. Intravenous urography may show calice distortion or cavities suggestive of tuberculosis pelvic lesions and kidney silence⁶.

Urine and lower urinary tract examination

Urinalysis may vary from mild changes, such as proteinuria and leukocyturia, to extreme pyuria, sometimes accompanied by hematuria. Urine cultures are regularly negative, unless there is severe bladder dysfunction. However, urine culture aimed at mycobacteria - using Lowenstein-Jensen solid culture medium - may be useful. In a study with 383 patients suffering from pulmonary tuberculosis, possible association with renal tuberculosis, suggested by the urinalysis, was found in 24 cases (6.2%), in which infection with *M. tuberculosis* complex prevailed (95.8%). The association between pulmonary and renal tuberculosis was found in 6 cases (1.5%). The isolation of *M. bovis* indicates the importance of including Stonebrink medium along with Lowenstein-Jensen medium¹¹. Multiple samplings should be obtained

in order to increase test sensitivity. Mycobacterium culture and identification results provide a specific diagnosis, yet may not be available for 2 to 3 weeks or longer. Polymerase chain reaction (PCR) techniques, such as the direct Gen-Probe MAD test, have been lately used. It is a reliable and fast-performing diagnostic test. Cystoscopy with biopsy is particularly recommended as it allows visualizing and sampling bladder lesions – this is possibly the best test to perform⁹.

Pathophysiology

Urogenital tuberculosis is always secondary to a respiratory inoculation, which may be clinically unapparent⁷. Bacilli reach the renal cortex by blood or lymphatic dissemination, where they thrive, before spreading to the lower urinary tract. The spreading lesions, most often bilateral, reach the pyramids, pelvis, ureters and bladder – seminal vesicles, epididymis and testicles may be also involved in advanced situations⁸.

Pathology

Typically, the initial lesion to be found in kidney biopsies is a granuloma with an area of central caseous necrosis and tubular-interstitial inflammation^{12,13}. Finding of acid-fast bacilli (which will be bright red on staining) by Ziehl-Neelsen stain inside the granuloma is clearly suggestive of tuberculosis. Yet, the finding of a diagnostic granuloma in a percutaneous kidney biopsy occurs by chance, as the disease is more often focal⁸.

Treatment

Urogenital tuberculosis treatment does not diverge from pulmonary tuberculosis therapy. Scarring and development of obstructive lesions may require surgical treatment, besides the placement of endoprosthesis in some special situations. Using a combination of the following drugs, according to the WHO recommendations⁷ – isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol hydrochloride and ethinamide – is currently recommended. It usually starts with a combination of isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1600 mg/day), and ethambutol (1100 mg/day) (“RIPE” schedule) for the first two months, followed by isoniazid (400 mg/day) and rifampicin (600 mg/day) for the next four months. The usual doses given above are for individuals weighing more than 50 kg¹⁴.

LEPTOSPIROSIS

Introduction

Leptospirosis is a zoonosis caused by organisms of the *Leptospira* genus, holding worldwide distribution. Its acute evolution, in humans, produces a variety of clinical manifestations, from nonspecific symptoms to profound jaundice, hemorrhages, meningeal symptoms and acute kidney injury (AKI). In a 10-year period (1996-2005), 33,174 occurrences were notified in Brazil, and during a single year (2007), 1,547 new cases were notified, mostly in the southern states¹⁴.

Clinical presentation

The clinical renal syndromes associated with leptospirosis are summarized in chart 1. Leptospirosis incubation period varies

from five to 14 days, with a median time of 10 days^{7,15}. Its clinical presentation varies, depending on the prevalent *Leptospira* serotype and the geographic area, from a febrile, almost asymptomatic condition, to a severe multisystem disease⁷. Its clinical presentation may occur as: (i) a non-jaundice, febrile, auto-limited disease (in 85-90% of instances); (ii) Weil's syndrome, with jaundice, AKI, hemorrhages and heart arrhythmias – myocarditis (in 5 to 10%); (iii) meningitis/encephalitis and???; (iv) pulmonary hemorrhages, with respiratory insufficiency. It usually follows a two-phase course: the first one (3 to 7 days) characterized by high fever (100-102° F), chills, and severe headaches; the second one in which anorexia, nausea, vomiting, diarrhea and intense myalgia, particularly in lower limbs, prevail. During the first phase it is possible to isolate *Leptospira* in blood samples. During the second phase IgM antibodies appear. Disease severity seems to depend on the intensity of the individual's humoral immune response¹⁵. The severest forms of the disease may lead to hemodynamic changes secondary to acute intravascular volume decrease, or a direct toxic effect upon vessels endothelium, and diffuse mounting of capillary permeability¹⁶. Pulmonary hemorrhagic syndrome may appear independently of other systemic symptoms, sometimes requiring mechanical ventilation, which leads to greater mortality risk¹⁷.

Chart 1 – Clinical syndromes in leptospirosis-associated kidney disease.

Clinical Presentation	Kidney Biopsy
AKI, Fever, jaundice, Myalgia, Headache, Vomiting, Dehydration, Chills, Calf pain, Diarrhea, Hepatomegaly, Anorexia, Oliguria, Tachypnea, Dyspnea, Crackles or rhonchi, Petechias, Arthralgias, Hemoptysis, Hematemesis, Conjunctival suffusion, Edema, Obtundation, Flapping, Constipation, Splenomegaly, Seizure	Acute tubular necrosis, Interstitial nephritis

AKI = acute kidney injury.

Kidney changes

The kidneys are almost always involved in severe leptospirosis. Non-oliguric leptospirosis-associated AKI is the most frequent presentation, usually accompanied by hypokalemia, opposed to AKI associated with other infectious diseases, such as malaria, diphtheria, or meningococcemia. Experimental, as well as clinical studies, have demonstrated that proximal tubule injury and collecting duct vasopressin blunted response may account for such metabolic alterations². Acute, severe jaundice has been linked to functional kidney changes that may encompass fall of glomerular filtration rate and reduced urinary concentration ability. Severe leptospirosis is frequently accompanied by intense jaundice, which may add to the development and severity of the AKI. Rhabdomyolysis and association with AKI is well established. Yet, how important rhabdomyolysis may be in leptospirosis-associated AKI is less evident. Increased serum creatinophosphokinase (CK) levels have been more often noticed in patients with severe leptospirosis-associated AKI than in those with less compromised renal function, suggesting an added risk for AKI from rhabdomyolysis². Proximal tubule damage and collecting duct vasopressin resistance reduce proximal sodium reabsorption and increase free-water clearance,

respectively - with resulting polyuria and enhanced natriuria². Increased distal tubule potassium secretion may be induced by increased sodium delivery to distal tubules and raised aldosterone and cortisol levels. Such findings point to a primary proximal tubule defect, with a comparative preservation of distal tubules functional ability to manipulate sodium and potassium. A prospective study on patients with leptospirosis-associated AKI found reduced proximal tubule sodium reabsorption, thus demonstrating the presence of a proximal tubule defect in these patients^{18,19}. Hypokalemia may occur in 45%-74% of patients at admission, potassium replacement being necessary in up to 80% of instances².

Diagnosis

During the initial febrile period, it is possible to visualize *Leptospira* by direct examination of blood, to grow it by seeding blood in adequate culture media, or to recover it by laboratory animal inoculation. As it might take several weeks to get a positive result from cultures, usually only a retrospective diagnosis may be obtained in this way⁷. During the second - immune phase - *Leptospira* may be found and grown from urine. Given the difficulties in obtaining a direct diagnosis, serologic tests, such as ELISA, IgM macro and microagglutination tests have been extensively performed⁷.

Pathophysiology

Several factors seem to be involved in the pathophysiology of the kidney lesion, such as a direct nephrotoxic effect by *Leptospira*, loss of salt and water, jaundice, and rhabdomyolysis. Experimental studies have suggested that lesions are associated with the physical presence of the organism in the kidney – *Leptospira icterohaemorrhagiae* has been visualized, as soon as 3 to 6 hours after inoculation, at the mesangium and interstitial tissue. It seems that glomerular capillary *Leptospira* passage is accompanied by a transitory, moderate, mesangial proliferation². Lack of hyperkalemia is remarkable, even in oligoanuric individuals, and is a significant characteristic of AKI in such a severe infectious disease. It should call the attention of an attending physician, whenever considering differential diagnosis of AKI. *Leptospira* outer membrane proteins (OMPs) may elicit tubular injury and inflammation through Toll-like receptors (TLRs)-dependent pathway followed by activation of nuclear transcription factor kappa B and mitogen-activated protein kinases and a differential induction of chemokines and cytokines relevant to tubular inflammation²⁰.

Pathology

Leptospira reach the interstitium by way of peritubular capillaries, causing an acute inflammatory response with focal interstitial edema, lymphocytes, macrophages, plasma cells and, occasionally, eosinophils infiltrate. Variable degrees of tubular necrosis are always present. *Leptospira* adhesion to tubule epithelial cells occurs early in the course of the disease, and the infecting organism may be detected even by light microscopy. Importantly, *Leptospira* antigens loading of tubular cells occur early in disease's course and may be detected by immunohistochemical staining techniques²¹.

Treatment

Quick clinical recovery is the usual outcome - serum creatinine returning to normal levels by the fourth to eighth day of symptomatic disease, depending on the severity of kidney involvement. Glomerular filtration rate, proximal sodium reabsorption, fractional potassium excretion, and tubular hydrogen generation complete recovery take place by the third month of follow up²². Yet, a concentration defect may persist for up to six months, and echoes the severity of AKI²². Penicillin seems to reduce symptoms and AKI severity; however, its advantage has been only demonstrated once started during the first week of infection^{23,24}. Early dialysis and treatment of *Leptospira*-associated AKI seems to be helpful in reducing mortality²⁵. Leptospirosis is a disease evolving with low mortality rate. However, in the presence of AKI, mortality rate may be as high as 22%². Previous studies have examined mortality risk factors associated with leptospirosis - oliguria, old age, episodes of cardiac arrhythmias, and pulmonary involvement are associated with poorer outcome - oliguria being present in over 50% of reported deaths².

LEPROSY

Introduction

Leprosy is a chronic disease caused by *Mycobacterium leprae* - an obligatory intra-cellular parasite that preferentially infects peripheral nervous system's Schwann cells and the skin⁷. Leprosy is currently reported in more than 100 countries. In 2009, a total of 244,796 new cases of leprosy were reported, and the prevalence at the beginning of 2010 was 211,903 cases²⁶. Kidney lesions have been demonstrated in all disease presentations, particularly in the multibacillary form^{27,28,29}. Recent studies show that renal involvement in leprosy is common, with proteinuria in 4.8% and hematuria in 6.8% of cases²⁹. Risk factors for kidney disease in leprosy include reaction episode, multibacillary classification and advanced age²⁹.

Clinical presentation

The clinical renal syndromes associated with leprosy are summarized in chart 2. Skin and peripheral nervous system damages are leprosy hallmarks. Apparently, host immune response seems to be determinant on the clinical pattern. Two different immunological complications in leprosy course may occur, sporadically intensifying symptoms: (i) a so called "reversal reaction" (type 1): a clinical presentation associated with paucibacillary leprosy pattern, and; (ii) "erythema nodosum leprosum" (type 2): frequently associated with multibacillary disease⁷. Leprosy has been classified in four different forms, according to WHO: indeterminate, tuberculoid, dimorphic and virchowian forms⁷. Diagnosis and classification are dependent upon the clinical presentation and laboratory tests - lesion direct bacilli count^{???} allows classifying leprosy lesions as pauci- or multibacillary.

Chart 2 – Clinical syndromes in leprosy-associated kidney disease.

Clinical Presentation	Kidney Biopsy
Polyarthrititis, Proteinuria, Hematuria, Urinary Concentration and Acidification defects, AKI, CKD	Diffuse proliferative lesion, Amyloidosis, Acute tubular necrosis, Crescentic nephropathy, Membranoproliferative nephropathy, Membranous nephropathy, Mesangial proliferative lesion, Interstitial nephritis, Glomerular sclerosis

AKI = acute kidney injury; CKD = chronic kidney disease.

Kidney changes

Kidney involvement reports started appearing around 1937, from autopsy studies of patients diagnosed as having died from leprosy²⁸. From then on, a series of autopsy and kidney biopsy studies have attempted to elucidate kidney involvement in leprosy. Acute and chronic, nonspecific, glomerular and interstitial lesions - besides amyloid deposits - have been linked to the disease. Glomerular involvement is the more prevalent structural change associated with leprosy, yet with a variable reported prevalence. Kidney biopsy studies on leprosy patients places prevalence at approximately 37%³⁰. Glomerular lesions were strongly associated with occurrence of erythema nodosum, even though lesions have also been reported with no such complication. Almost all known morphological glomerular lesions have been reported, except for focal segmental glomerular sclerosis (FSGS)³¹. Yet membranoproliferative glomerulopathy, so often associated with infectious diseases, has been reported slightly more frequently than other forms³¹.

Pathophysiology

Mechanisms leading to leprosy-associated glomerular lesions have been only partly elucidated. Despite bacilli being found in glomerular lesions, no clear evidence for direct *Mycobacterium leprae* involvement in their genesis exists. Immunological mechanisms may be required: serum complement may be reduced; subendothelial immune complexes have been demonstrated by electron microscopy; IgA mesangial deposition has also been detected. Circulating immune complexes typically accompany erythema nodosum leprosum, with its conceivable deposition in vessels and tissues, including glomeruli. *Mycobacterium leprae* antigens may be freed, once antibiotics are initiated³². Alternatively, antibodies directed toward antigens somewhere inside the glomerulus may complex and deposit locally³². However, not every leprosy-associated kidney lesion relates with the concomitant development of erythema nodosum leprosum, thus suggesting glomerular lesions are of multifactorial origin. Significant reduction on cellular immune response occurs in virchowian leprosy with humoral immune response hyperactivation, which might facilitate immune complex formation and development of glomerular lesions³⁰.

Tubular dysfunction occurs with some frequency (from 25% to 85%), either in multi- or in paucibacillary leprosy⁵. Urine acidification defect appears in 20% to 32%, whereas inability to concentrate urine may occur in up to 85% of leprosy patients⁵. Immunohistochemical examination of kidney samples identified IgM, C3 and, less often, IgA and IgM deposits in the mesangium and capillary basal membranes³³. Electron microscopy substantiate the presence of mesangial and subendothelial, or sub-epithelial, granular dense-deposits³⁰. The complement may be reduced in some patients, supporting the idea of an immune-mediated lesion³⁰.

Urine changes

Leprosy has often been associated with hematuria, especially in its virchowian form, and with erythema nodosum leprosum, even in the absence of glomerular changes. Microscopic hematuria accompanies virchowian form leprosy in 12 to 17% of

instances – it often disappears after a couple of months on treatment³⁰. Several studies have reported the occurrence of proteinuria (from 2 to 68%), more frequently associated with immunological complications of multibacillary disease³⁰. It usually varies from 0.4 to 8.9 g/24-hour, yet nephrotic syndrome is an unusual presentation. Virchowian form leprosy is more frequently associated with proteinuria and presence of leukocytes, red blood cells and casts in urine, being uncommon in other forms of the disease⁵.

Pathology

Glomerular lesions

Renal tissue reaction to *M. leprae* could be induced by various local immunologic or physiological factors. The great variety of lesions suggests a heterogeneous disease, though dependent on a single cause – immune complexes quantity and quality may stand for a divider^{5,32-34}. Adequate kidney biopsy was obtained from 54 cases of leprosy: 45 were lepromatous form, 4 tuberculoïd and 5 belonged to borderline form of leprosy. Membranous nephropathy in 17 (32%) was the commonest type of glomerular lesion followed by diffuse proliferative lesion in 12 (22%), membranoproliferative lesion in 6 (11%); two samples presented a crescentic nephropathy. Specific glomerular lesions in leprosy include epithelioid granuloma with Hansen's bacilli in the kidney³³. Diffuse, endocapillary, proliferative process, with numerous neutrophils occluding peripheral capillary loops, can also be found in leprosy³⁴. Electron microscopy may show immune complex-type, electron-dense deposits in the subendothelial area, with electron-dense humps³⁵. Crescent formation has also been described in leprosy³⁶.

Tubulointerstitial lesions

Interstitial nephritis has been reported chiefly in patients with lepromatous leprosy and seems to relate with long-term illness and extended therapy - such lesion may be the most regular histological finding in leprosy³⁷.

Chronic kidney disease and leprosy

End-stage renal disease (ESRD) has been reported as a cause of death in patients with leprosy³⁸. ESRD in leprosy has been associated with amyloidosis, more often accompanying virchowian form leprosy³⁴. Amyloid has been detected in as short an evolution period as two years, suggesting that a long disease course may not be necessary for its development³⁹. Elevated serum amyloid A levels have been shown during episodes of immunological complications and remained elevated for several months³⁹. In India, where leprosy prevalence is high, almost 50% of patients have some renal abnormality, yet ESRD has seldom been a cause of death³⁹.

Drug-associated renal changes

Despite renal changes associated with drugs used in leprosy therapy being unusual, acute kidney injury (AKI) described as acute tubular necrosis, acute interstitial nephritis, or papillary necrosis have been reported²⁹. Both rifampicin (intermittently, in high doses) and dapson have been implicated in interstitial nephritis and intravascular hemolysis with AKI³⁰.

Treatment

The World Health Organization-standardized leprosy therapy includes rifampicin, dapson and clofazimine. Prednisone (1 to 2 mg/kg/day) and non-steroidal anti-inflammatory drugs (NSAI) may be used to control acute immunological episodes. Erythema nodosum leprosum (ENL) may sometimes have a protracted course (months, or years) and is usually treated with NSAIDs, steroids, thalidomide, clofazimine and pentoxifyline. The management of ENL can be done with corticosteroids alone, or corticosteroids and clofazimine. The ideal dose of corticosteroids is not well established, but it should not exceed 1mg/kg body weight, with a total duration of 12 weeks. The addition of clofazimine (100 mg three times a day, for a maximum of 12 weeks) to corticoids is indicated when severe ENL is not responding satisfactorily to treatment with corticosteroids. Analgesics can be used to control fever and pain. Multidrug therapy for leprosy should be continued¹⁴.

MALARIA

Introduction

Malaria is the global most prevalent infectious disease and, consequently, of extreme epidemiological concern. Its infective agents are *Plasmodium* genus protozoae. Four different species have been associated with the human disease: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*⁷. Kidney disease is more frequently associated with infection by *P. falciparum* and *P. malariae*⁷. *P. falciparum* is highly prevalent in tropical areas, developing progressively increased drug resistance. *P. falciparum* infection may be accompanied by AKI in 1% to 4% of cases. Additionally, immune-mediated glomerular lesions have been associated with *P. falciparum* infection. According to WHO surveys, its incidence varies between 0.3 and 0.5 billion new cases/year, leading to between 1.5 and 2.7 million deaths, especially among children below age five. In Brazil, 97% of diagnosed patients concentrate in the Amazon rural areas¹⁴.

Clinical presentation

The clinical renal syndromes associated with malaria are summarized in chart 3. Malaria transmission usually occurs when parasite *sporozoite* forms enter human host blood through the bite of an infected female *Anopheles* genus mosquito. Malaria may follow an acute - sometimes vicious - or a chronic course. Weakness, anorexia, myalgia, headache, nausea and vomiting are frequent presenting symptoms, besides fever, chills and sweating, which may recur daily or up to every fourth day. Anemia, with enlarged liver and spleen, soon turns up. In malaria *fulminans*, caused by *P. falciparum* infection, patients develop anemia, weakness, diarrhea, jaundice, coagulation defect, AKI, acute respiratory failure and coma, accompanied by severe electrolyte disturbances. Infection by either *P. ovale* or *P. vivax* may undergo reactivation, once quiescent *hypnozoite* forms harbored in the liver appear. Wasting, fever, anemia, liver and spleen enlargement follow. Jaundice almost always occurs in malaria with AKI. Nephritic or nephrotic syndrome may be the clinical depiction. However, differently from kidney involvement in *P. malariae* infection, *P. falciparum* glomerular lesions disappear between 2 and 6 weeks from parasites eradication⁴⁰.

Chart 3 – Histological findings in *P. falciparum* kidney disease.

Structure	Pathology	Clinical Presentation	Pathogenesis
Glomeruli	OM: light mononuclear infiltrate; prominent mesangial proliferation; mesangial matrix expansion; parasite-loaded red blood cell in glomerular capillaries. IF: IgM and C3 mesangial and capillary walls granular deposits; glomerular endothelial cell and medullar capillaries malarial antigens detection. EM: subendothelial electron-dense deposits, amorphous, fibrillar or granular mesangial deposits.	Mild proteinuria, hematuria and hyaline casts. No progression to kidney failure; remission with specific therapy. Nephrotic and nephritic syndrome: rare. Hypertension: seldom	Immune complex-mediated
Tubules and Interstitium	Patients with uncomplicated <i>F. malariae</i> disease presenting mild proteinuria: no tubular or interstitial lesion; patients with AKI: tubular cells with vacuolization or “bald tubules”, hemosiderin casts, interstitial edema, mild to moderate interstitial mononuclear infiltrate	AKI in 1% to 4%; above 60% in severe disease. Associated with intense parasite blood load or intravascular hemolysis (with or without G-6PD deficiency). Usually between 4-7 days after starting fever. Oliguria (days to weeks) and increased catabolism (BUN/Cr>15), severe hyperkalemia, hyperuricemia and jaundice	Kidney ischemia induced by parasite-loaded red blood cells, cytokines and acute phase inflammatory response factors
Vessels	No significant changes. Parasite-loaded red blood cells in peritubular capillaries and venules.		

OM = optical microscopy; IF = immunofluorescence; EM = electron microscopy; BUN = blood urea nitrogen; Cr = creatinine.

Diagnosis

The laboratory diagnosis of malaria depends upon demonstration of the parasite in blood. However, several immunological tests are currently available and useful.

Kidney pathology and pathophysiology

Independently of age, *P. falciparum* glomerular lesions are quite uncommon in adult patients, yet less so in children³⁹. Incidence of glomerular involvement in *P. falciparum* is uncertain (18% previously reported); microalbuminuria, mild to moderate proteinuria, hyaline and cellular casts were reported in 20% to 50% of all affected individuals⁴¹. Nephrotic syndrome has seldom been detected. However, AKI is a frequent kidney involvement presentation of malaria. Acute tubular necrosis with blood casts, diffuse interstitial infiltrates and edema, microscopically characterize kidney lesions⁴². Tissue damage progression to AKI is complex and possibly includes the interaction of mechanical and immunological factors, – cytokines and acute phase inflammatory response factors⁴². *P. malariae* has been associated with glomerular lesions more frequently than other species. Proteinuria has been found in 46% of patients harboring *P. malariae*, occasionally accompanied by microscopic hematuria⁴¹. Complement is not usually depressed. On electron microscopy, immune deposits may be seen in association with membranoproliferative glomerular lesions⁴¹. Nephrotic syndrome may appear several weeks after the infection starts⁴¹.

Malaria kidney injury is primarily due to red blood cell changes, as well as Th1 and Th2-cell activation⁴². It has been proposed that preferential Th2-cell stimulation leads to complement cascade activation, glomerular immune deposits, and glomerular injury. Otherwise, parasitic proliferation making red blood cells to massively burst may induce AKI - as seen in *P. falciparum* infections. When Th1-cell activation predominates, acute interstitial nephritis or acute diffuse proliferative lesion may be seen⁴². Several factors may contribute to such

outcomes, such as reduced circulating blood volume, generalized vasoconstriction, red blood cells lysis, with hemoglobinuria, immune complex glomerular deposits, microcirculatory dysfunction induced by parasite-modified erythrocytes and, less often, rhabdomyolysis⁴⁰. Few studies have evaluated glomerular involvement in *P. falciparum* malaria. Several histological patterns can be identified, including glomerular lesions, acute tubular necrosis and interstitial nephritis, either isolated or in association, yet basal membrane modifications have not been demonstrated; blood vessels with parasite-laden erythrocytes have been occasionally spotted⁴². Previous studies have demonstrated glomerular changes in *P. falciparum* infection: conspicuous mesangial cell proliferation, and moderate mesangial matrix expansion with occasional basal membrane thickening. Capsular, endothelial and mesangial granular eosinophilic deposits were also identified. IgM, C3 and parasitic antigens could be demonstrated as immunofluorescent deposits⁴². Subendothelial and mesangial electron-dense deposits, associated with amorphous granular or fibrillar material, were also demonstrated on electronic microscopy⁴². Tubular changes include hemosiderin granular deposits, hemoglobin casts, interstitial edema and mononuclear cell interstitial infiltrates. In 1 to 4% of *P. falciparum* affected patients, acute tubular necrosis occurs⁴³. It usually presents as oliguric AKI, sometimes associated with intravascular hemolysis and coagulation, or rhabdomyolysis⁴³. Membranoproliferative glomerular lesion has also been associated with *P. malariae* infection. On electron microscopy, basal membrane segmental thickening with subendothelial deposits creates a typical double contour image, accompanied by mesangial proliferation. Occasionally, capsular epithelial crescent formation may be seen, more often so in adults⁴². Progression to glomerular sclerosis may occur. Quite possibly, glomerular immune complex deposits require formation of antigen-antibody combinations involving parasite antigens⁴².

Treatment and outcome

Chloroquine is the foremost drug used in malaria treatment. However, some strains of *P. falciparum* may be chloroquine-resistant. Primaquine, quinine and mefloquine may be used, isolated or in association. Early dialysis has been suggested for patients presenting with AKI. As in other situations associated with AKI, outcome depends on the severity of systemic involvement, and mortality may be as high as 30%⁴⁰.

VISCERAL LEISHMANIASIS (KALA-AZAR)

Introduction

Visceral leishmaniasis is a chronic, lethal, parasitic disease, caused by *Leishmania* parasite, an intracellular protozoa. A large spectrum of clinical manifestations accompanies *Leishmania* assault on reticuloendothelial tissues - liver, spleen, bone marrow, lymph nodes and digestive system. Symptoms range from irregular and recurrent fever to pancytopenia, hemorrhagic spells, liver and spleen enlargement⁷. Kidney involvement in chronic leishmaniasis is frequent, and associated with increased mortality. It is endemic in southern Europe and in tropical and sub-tropical areas of the globe, with incidence reaching approximately 0.5 million/year⁴⁴. When untreated, its mortality may reach 95%. Among the so called tropical diseases, Kala-azar is one of World Health Organization's priorities. Endemic in Brazil, its agent is *Leishmania chagasi*. Humans are infected through the vector insect *Lutzomyia longipalpis*⁴⁵. Diagnosis of Kala-azar is confirmed by demonstrating the parasite in tissues using Giemsa stain, besides detection of parasite antigen K-19⁷.

Kidney involvement

Patients presenting with chronic Kala-azar may have mild proteinuria, microscopic hematuria and leukocyturia. Hypoalbuminemia, hypergamma globulinemia, as well as increased plasma levels of both IgG and b2-microglobulins were found in a group of 55 patients with visceral leishmaniasis⁴⁶. Increased albumin excretion was observed in 44% of patients. Proteinuria consisted predominantly of low molecular weight protein fractions that migrated with alpha1, alpha2, beta and especially gamma globulins. Urinary b2-microglobulin excretion was elevated in all patients. Microalbuminuria was detected in more than 40% of patients with visceral leishmaniasis, even in those with normal creatinine levels⁴⁷. Interstitial nephritis with glomerular changes may be seen. A mesangial proliferative lesion is often found, yet a membranoproliferative lesion is not rare⁷. Additionally, amyloid deposits may occur in chronic disease. However, renal involvement is usually mild and transitory. Loss of kidney function, and urine sediment changes, have been reported in visceral leishmaniasis. Kala-azar prospective studies have demonstrated that hematuria, mild to moderate proteinuria, and increased urine leukocytes, appear in over 50% of instances⁴⁸. A large, retrospective study demonstrated that more than 11% of patients with chronic *Leishmania* disease have decreased filtration rate at hospital admission - with anti-parasitic therapy, changes disappear. Chart 4 depicts known kidney involvement in Kala-azar. Interestingly, hypoalbuminemia, polyclonal hypergammaglobulinemia and leucopenia usually occur in chronic leishmaniasis⁷.

Other less frequent disorders have been described in visceral leishmaniasis, including hormones and electrolyte abnormalities. In a study

Chart 4 – Clinical syndromes in visceral leishmaniasis-associated kidney disease.

Clinical Presentation	Kidney Biopsy
AKI, Proteinuria, Nephritic syndrome, Nephrotic syndrome, Urinary Concentration and Acidification defect	Interstitial nephritis Diffuse proliferative lesion, Collapsing FSGS, Necrotizing FSGS, Membranoproliferative lesion, AA amyloid glomerular deposits, Chronic tubulointerstitial nephritis, arteriosclerosis, Tubular atrophy, interstitial fibrosis, mononuclear infiltrate, mesangial hyperplasia, peritubular Leishmania-loaded histiocytes Moderate to severe lymphocyte, histiocytes and plasma cells interstitial infiltrates

FSGS = focal segmental glomerular sclerosis; AKI = acute kidney injury.

by Lima Verde et al, with 72 patients with visceral leishmaniasis, plasma ACTH (corticotrophin) was found to be significantly higher among patients in comparison to normal subjects, as well as plasma renin activity. Primary adrenal insufficiency was observed in half of the patients; they present low aldosterone/renin plasma ratio, low daily urinary aldosterone excretion and low transtubular potassium gradient. In the same study all patients had normal plasma antidiuretic hormone (ADH) concentrations, hyponatremia, high urinary osmolality and more than half of the patients had low plasma parathyroid hormone and hypomagnesemia. In another study from the same group, with 55 patients with visceral leishmaniasis and 20 normal individuals, hyponatremia and high urinary sodium was detected in all patients suggesting a persistent antidiuretic hormone secretion with no evidence of extracellular volume depletion. Normal plasma ADH levels were observed in kala-azar patients. The syndrome of inappropriate antidiuretic hormone secretion could be responsible for these findings⁴⁹. Electrolyte disturbances found in patients with visceral leishmaniasis include hyponatremia (94.6%), hypokalemia (26%), hypochloremia (27.2%), hypocalcemia (32%), and hypomagnesemia (41.8%)⁴⁴. Urinary concentration and acidification defects were also found in patients with visceral leishmaniasis⁵⁰.

There are some differences between adults and children with visceral leishmaniasis. The time between onset of symptoms and beginning of treatment is longer in adults (89.5 vs. 48.5 days, $p < 0.001$). Failure of treatment with glucantime is more common in adults (17.6% vs. 8.8%, $p = 0.008$). Acute kidney injury associated with visceral leishmaniasis, which was observed in 37% of cases, is more severe in adults. Risk factors for AKI in adults were hypokalemia, leukopenia, chills and amphotericin B use. In children, secondary infections were found to increase the risk for AKI⁵¹.

AKI can be found in a significant proportion of patients with visceral leishmaniasis^{52,53}. In a study with 146 children with visceral leishmaniasis, AKI was found in 45.9% of cases. Patients in the AKI group were significantly younger, had jaundice and secondary infections more often than non-AKI patients. The AKI group had significantly lower serum sodium, potassium, serum albumin, elevated serum globulins and a more prolonged prothrombin time. The risk factors for AKI were secondary infections (OR: 3.65, $p = 0.007$), serum albumin decrement (OR: 1.672, $p = 0.019$), and high serum globulin (OR: 1.35, $p = 0.029$)⁵². In a study with 224 adults with visceral leishmaniasis, AKI was observed in 33.9% of cases, and the risk factors for AKI were male gender (OR: 2.2; $p = 0.03$), advanced age (OR: 1.05; $p < 0.001$), and jaundice (OR: 2.9; $p = 0.002$).

Pathophysiology

Most parasitic diseases evolve into chronic illness, with fluctuation in antigenemia and in host response. Several possible explanations are possible, such as low natural immune response, or parasite's ability to evade host immune system attack. It has been demonstrated that development of host resistance is usually dependent upon T-CD4+ cells producing interferon γ (IFN- γ) - a TH1-type cell. However, a mixed TH1 and TH2 response seems to be involved in extracellular parasites eradication⁵⁴. The *Leishmania* is able to manipulate the host immune system by inducing production of growth-factor b, a macrophage-inhibiting cytokine, and interleukin-10, besides interfering in IFN- γ signaling, all affecting cellular immune response and inducing polyclonal B-cells activation, which has been associated with Kala-azar glomerular disease⁵⁴. Antibodies produced in response to infection may be trapped in glomeruli by different mechanisms, such as immune complexes, *in situ* development of complexes (antibodies linked to previously implanted glomerular antigens), or directly attached to glomerular antigens. However, recent studies demonstrated that antibodies alone do not explain the occurrence of proteinuria^{54,55}. Macrophages, granulocytes, natural-killer lymphocytes are all part of host defenses, and participate on the genesis of glomerular lesions through an intricate chain of cytokines and inflammatory mediators, as evidenced experimentally^{54,55}. It is possible that reduced tubular concentration and acidification functions are caused by IgG overload of tubular cells, in patients presenting with major globulins plasma level changes⁵⁶. A distal tubule acidification defect may occur.

Histopathology

Mesangial proliferative, membranoproliferative, and collapsing FSGS seem to be the more frequently seen patterns associated with Kala-azar nephropathy, the severity of which may vary from mononuclear interstitial infiltration to a severe, diffuse, inflammatory infiltrate composed by macrophages, lymphocytes and plasma cells⁵⁷. On immunofluorescence microscopy, IgG, IgM, IGA and C3 deposits in the mesangial matrix may be found⁵⁷. Experimentally, tubular and interstitial lesions have been the most frequently Kala-azar-associated kidney lesions. However, amyloid deposits, rapidly progressive glomerulonephritis with the nephrotic syndrome, have been reported in human leishmaniasis^{58,59}. Experimental infection by *L. donovani* may end-up with amyloid deposition, following an initially diffuse proliferative glomerular lesion⁶⁰. The finding of *amastigote* forms in the kidney is a rare event, yet it is possible to identify *Leishmania* antigens in inflammatory infiltrates⁵⁴.

Treatment and evolution

Pentavalent antimony compounds are still the drugs of choice in treating visceral leishmaniasis. However, amphotericin B may be equally effective. Usually, the kidney changes disappear soon after infection control.

SCHISTOSOMIASIS

Introduction

Schistosomiasis is a parasitic disease produced by parasites of the genus *Schistosoma*. Three main species - *S. Mansoni*, *S. japonicum* e *S. haematobium* -, and two other with restricted distribution - *S. mekongi* e *S. intercalatum* - are the causative agents of human

disease⁷. The parasite's adult forms infest its final host mesenteric vessels. *S. mansoni* is usually found in South America and the Caribbean, *S. haematobium* in Africa and Middle East, *S. intercalatum* in several areas of southeast Asia and *S. japonicum* in China and the Philippines⁷. The disease has been registered in 74 different countries in tropical areas, especially in Africa, East Mediterranean and South America. Globally, more than 200 million individuals are infected, 120 million will develop symptoms, 20 million progresses to severe illness, and 100,000 die each year due to schistosomiasis⁷.

Clinical presentation

Schistosomiasis is a variably severe, chronic illness, humans being its ultimate host. The adult parasite occupies liver and spleen vessels, with evolution depending upon host's immune response¹⁴. Most infected individuals remain asymptomatic. Typically, the disease follows a two-phases course: i) early infection - *cerariae* skin penetration, characterized by allergic symptoms, including skin rash, followed by fever, headache, anorexia, abdominal pain, swollen lymph nodes and, eventually nausea, vomiting, diarrhea and dry cough; ii) a late course - usually starting after six months, and lasting for several years, with pulmonary and portal hypertension, ascitis and esophageal varicosities¹⁴. Increased blood eosinophils are usually present⁷.

Kidney involvement

S. mansoni

Kidney involvement in all forms of schistosomiasis has been estimate to be around 5 to 6%, reaching up to 15% when liver and spleen are compromised⁶¹. Glomerular lesions have been demonstrated in 10 to 12% of autopsy cases. As much as 20% of *S. mansoni* infected patients present with proteinuria⁶². Schistosomiasis glomerulopathy may be initially symptomless, evolving into proteinuria and nephrotic syndrome, or non-nephrotic proteinuria and microscopic hematuria. A small percentage of patients may progress to chronic kidney disease⁶². Kidney biopsy may show basal membrane deposition of immune complexes holding *Schistosoma* antigens⁷. *Schistosoma* ova deposition-associated granulomas have been reported in kidney tissue⁶³.

Pathophysiology

Pathophysiology of glomerular lesions holds some similarities with malaria. It seems to depend upon development of immune mechanisms. Presence of parasite antigens appear to be related with occurrence of glomerular disease, such finding having been demonstrated in experimental and clinical events of *S. mansoni* infection^{64,65}. *Schistosoma* antigens have been detected in kidney tissues in 44% of patients with moderate proteinuria, and in 63% of those with the nephrotic syndrome, and advanced kidney disease⁶⁶. Circulating immune complexes bearing parasite antigens, as well as *Schistosoma* antigen-containing glomerular deposits, have been reported, strengthening the impression of immune-mediated lesions⁶⁷. Anti-DNA antibodies have been found in *S. japonicum*-infected hamsters, suggesting that development of such antibodies could play a role in B-lymphocytes activation⁶⁸. Apparently, the level of proteinuria and the severity of kidney disease correlate with the intensity of liver macrophages dysfunction⁶⁹.

Pathology

Mesangial proliferative and membranoproliferative glomerular lesions have been more often seen in patients presenting with liver and spleen schistosomiasis⁶¹. The mesangium is the glomerular structure usually involved in kidney schistosomiasis. Mesangial matrix expansion, accompanied by mesangial cells hypertrophy and hyperplasia, granular dense-deposits in subendothelial and mesangial location may be seen⁶¹. IgM, IgG, C3 and, occasionally, IgA deposits may appear by immunofluorescence examination⁶¹. Experimentally, mesangial proliferative lesion is the predominant variety of glomerular lesions – *Schistosoma* antigens having been identified even without the accompanying antibodies, suggesting their being embedded in the glomerular structures⁶¹. Membranous disease is rarely seen, its relationship with schistosomiasis doubted on clinical and experimental data. Amyloid renal disease is rarely seen in association with schistosomiasis and other parasitic diseases⁶¹. In a recent Brazilian study, 8/63 individuals had abnormal albuminuria. On kidney biopsy, mesangial expansion was evidenced in all; mesangial cell proliferation was visible in 5, and basal membrane duplication in 4 patients. Focal and segmental glomerular sclerosis appeared in 4 patients⁷⁰. Electron microscopy revealed subendothelial electron-dense deposits with predominantly IgG and IgM deposition, and occasional IgA and C3, along the basal membrane⁷⁰. Additionally, minimal changes nephropathy may occur in asymptomatic individuals; yet mesangial proliferation has prevailed⁶². Based on pathology findings, a five categories classification of schistosomiasis nephropathy has been proposed: i) mesangial proliferative lesion; ii) membranoproliferative nephropathy; iii) FSGS; iv) exudative glomerulitis; v) amyloid deposit⁷¹. Patients presenting with mesangial proliferative lesions are usually asymptomatic or have mild proteinuria and microscopic hematuria, yet may evolve into full nephrotic syndrome and ESRD⁷². Patients showing membranoproliferative changes usually present with low CH50, C3 and C4 levels, suggesting a classical activation of the complement system. It has been demonstrated that mesangial proliferative lesions may undergo transformation into membranoproliferative lesions⁷³. Ruling out Hepatitis B and C virus infection is mandatory. FSGS was the only lesion identified in 11 to 38% of infected individuals – lesions not significantly differing from the idiopathic variety⁷². Kidney lesions being a primary tissue response to *Schistosoma* infection – as in HIV virus infection –, or focal and segmental scarring of prior mesangial proliferative lesions have been subject of speculation⁷³. Other pathological pictures have occasionally been reported⁷³.

Evolution and treatment

Several previous studies suggest that schistosomiasis kidney lesions may be irreversible, possibly because lately identified⁶². That is particularly so when proliferative lesions occur⁶⁰. All infected patients should be treated to eradicate the parasite. Two drugs are currently available for schistosomiasis therapy: praziquantel (single dose – 50 mg/kg) and oxaminiquine (single dose - 15 mg/kg). Frequent adverse effects are nausea, dizziness and skin rash¹⁴.

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