www.nephropathol.com DOI: 10.5812/nephropathol.8111 J Nephropathology. 2012; 1(3): 155-159

Journal of Nephropathology

See Brief Report on page 188

Mucormycosis and acute kidney injury

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ARTICLE INFO

Article type:
Commentary

Article history:
Received: 3 August 2012
Accepted: 6 August 2012
Published online:
1 October 2012
DOI: 10.5812/nephropathol.8111

Keywords:
Mucorales
Renal mucormycosis
Acute kidney injury

ABSTRACT

Mucormycosis, although said to be less common than candidiasis and aspergillosis is becoming increasingly associated with many co-morbid conditions and immunosuppression. Renal involvement, rarely reported previously, has also been documented with increasing frequency in recent times in both diseased as well as apparently healthy individuals. The kidneys may be involved in disseminated disease or have an isolated involvement for unexplained reasons. The manifestations are very serious particularly in patients with bilateral renal mucormycosis who often develop acute kidney injury and usually have a fatal outcome. The diagnosis of the renal mucormycosis is based on renal histology sections of renal biopsy or nephrectomised kidneys. Imaging with computerised tomography with contrast is of tremendous help in early identification of these cases before histological diagnosis. Once diagnosis is established, prompt treatment with antifungal medication, including Amphotericin-B (and its lipid formulations) and posaconazole, and removal of infected tissue is necessary to save from otherwise fatal infection.

Commentary

Implication for health policy/practice/research/medical education:
Renal mucormycosis is often seen in patients with immunocompromised status. The disease may manifest with serious renal manifestations including flank pain, hematuria, pyuria and acute kidney injury particularly in patients having bilateral renal involvement with nearly universal fatal outcome. Hence an early diagnosis is very important with awareness of its manifestations, imaging and renal histology. Appropriate antifungal therapy with nephrectomy can save many patients with renal mucormycosis.

Please cite this paper as: Gupta KL, Gupta A. Mucormycosis and Acute Kidney Injury. J Nephropathology. 2012; 1(3): 155-159. DOI: 10.5812/nephropathol.8111

Mucormycosis, is an invasive fungal infection caused by the filamentous fungi belonging to the Class Zygomycetes, Order, Mucorales and its 4 genera Rhizopus, Mucor, Absidia, and Saksenaea (1). Species of 3 more genera, Rhizomucor, Apophysomyces, and Cunninghamella, although less common, have also been documented to be pathogenic to human beings (2). These fungi are ubiquitous in nature and are distributed in soil, decaying vegetation, hay, stored seeds or horse manure outdoors and in house dust, and poorly maintained vacuum systems or dirty carpets indoors (3, 4). Mucor can be easily recognized in the labora-

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tory media by its tall needle like sporangiophores and large sporangium. It can reproduce asexually with spores, or sexually by fusing to create zygospores which contain a mixture of genetic material (1). The term mucormycosis has undergone many transformations since its first description in 1885 by Paltauf (5). It was termed phycomycosis and then zygomycosis till recently when it was renamed as mucormycosis on the basis of fungal taxonomy (2). Although nosocomial in distribution, mucorales can cause serious deep-seated infection in immunocompromised conditions such as diabetic ketoacidosis, hematologic malignancies or solid cancers, immunosuppressive therapy after solid organ or bone marrow transplantation, acquired immunodeficiency syndrome (AIDS), severe malnutrition, chelation with deferoxamine and many other debilitating conditions (1). Classically, invasive mucormycoses been classified into six different clinical syndromes based on the general location of the disease: rhino-cerebral, pulmonary, gastro-intestinal, cutaneous, disseminated and miscellaneous (6). Rhino-cerebral mucormycosis is the most common form seen primarily in uncontrolled diabetic patients. It involves the sinuses, orbits, eyes, brain, cranial nerves, hard and soft palates, both mandibles and the rest of the face. Pulmonary mucormycosis is the second most common form seen usually in patients with haematological malignancies. It occurs by inhalation or hematogenous or lymphatic spread. Gastrointestinal mucormycosis is relatively rare and thought to be caused by ingestion of zygospores especially in the malnourished and alcoholics. Cutaneous mucormycosis occurs when the intact skin barrier is disrupted by skin maceration, burns or trauma. Disseminated mucormycosis is the form that has the worse prognosis and it usually follows severe fungemia in immune compromised individuals with subsequent hematogenous spread to many body organs including brain, heart, lungs, and kidneys among others. Miscellaneous mucormycosis involving any part of the body like bone, skeletal system or urinary tract, can cause disastrous consequences in the affected site (1, 6).Renal involvement is less common although it has been reported in up to 14% in a single centre study from India (7). It occurs in 22% of disseminated mucormycosis (8) but isolated renal mucormycosis has also been documented as case reports (9-13) or case series (14, 15). Isolated involvement may be haematogenous in origin from a subclinical pulmonary focus without manifestation in the lung akin to renal tuberculosis (16), or may result from an ascending infection of the urinary tract (17). Rarely, kidney may be involved by contiguous spread from overlying infected incision (18) or from infected donor in renal transplant recipients (19). As the *mucorales* infections have an almost universal feature of extensive angioinvasion associated with thrombosis and ischemic necrosis, kidneys are similarly involved in the process with consequent complications (1). Some data have also demonstrated the ability of R. oryzae sporangiospores or hyphae to adhere to subenthodelial matrix proteins and human endothelial cells (20).The clinical manifestations of renal mucormycosis depend upon whether the disease is unilateral or bilateral and whether it is disseminated or isolated to the kidney (6,7). The common clinico-laboratory features in this condition described by Gupta et al. (15), were fever (88%), flank pain and tenderness (70%), haematuria and pyuria (70%), and concomitant bacterial urinary tract infection (53%). Acute renal failure was observed in 92% of patients with bilateral renal involvement. As emphasized by these authors, mucormycosis is being increasingly encountered as a cause of otherwise unexplained

acute renal failure. Besides the case reported in this issue (21), there have been many similar cases reported in literature (15, 17, 22, 23). Renal failure is usually the result of near total occlusion of the renal arteries and/or their branches (15). Both small and large arteries exhibit hyphal invasion and consequent thrombosis leading to massive cortical and medullary infarction (11, 23). These findings have been confirmed in the kidney biopsy of these patients and at autopsy (23). Besides the extensive ischemic destruction of parenchyma, the histological findings may include the invasion of the glomeruli and tubules by the mucor hyphae (15). There may be associated giant cell reaction with formation of granulomas in some cases (17). The mucorales are recognized in Groccot's silver methanamine stained slides by their characteristic morphology (24). These fungi have broad aseptate hyphae which branch irregularly at right angles as against the septate dichotomously branching hyphae of Aspergillus (1). Differential diagnosis of acute kidney injury in these patients may be severe pyelonephritis, acute interstitial nephritis and rapidly progressive glomerulonephritis (23). One can make the correct diagnosis of this condition only if it is suspected early and investigated with laboratory and imaging tests. Since histology is the 'gold standard' of diagnosis, an attempt should be made to get the biopsy of the infected tissue without delay. Culture of various body fluids and infected tissues may be sent although it is very uncommon to grow mucorales in culture (24). Imaging can be a useful diagnostic modality to enable early diagnosis of renal mucormycosis. Besides the ultrasonography suggesting enlarged kidneys, contrast enhanced computerized tomography may reveal the typical features reported earlier (25). Very recently molecular diagnosis with real time PCR has been suggested for an early diagnosis of this condition (24).

Treatment

Prognosis of renal mucormycosis is dismal with nearly 100% mortality in patients with bilateral renal involvement and acute kidney injury (15). Majority of survivors of renal mucormycosis have been those with unilateral renal involvement who received timely appropriate antifungal therapy with nephrectomy. Few exceptions have also been reported in patients with bilateral renal mucormycosis with successful outcome following bilateral nephrectomy and antifungal therapy (13) or medical therapy alone (26). The four cornerstones of successful therapy are 1) rapid initiation of therapy, 2) reversal of the patient's underlying predisposing condition, 3) administration of appropriate antifungal agents, and 4) surgical debridement of infected tissues i.e. nephrectomy (27). Only 2 systemic antifungal drugs are currently available with good activity against mucorales; Amphotericin B (including the lipid formulations) and the triazole, Posaconazole. Amphotericin-B continues to be the gold standard of antifungal therapy but the conventional formulation is associated with a high incidence of adverse events and resistance in some cases. Patients with renal mucormycosis may benefit from its lipid formulations in view of renal failure that these patients usually have (28). In addition, we can give higher dose of Amphotericin with lipid formulation for a faster control of disease. Posaconazole, a new triazole, with its pharmacokinetic advantages and low side effect profile, has been increasingly used in mucormycosis both as a "step-down" therapy following initial amphotericin administration and as a "salvage" therapy in patients with resistance to Amphotericin B (29).

Summary

Renal mucormycosis is often seen in patients with immunocompromised status. The disease may manifest with serious renal manifestations including flank pain, hematuria, pyuria and acute kidney injury particularly in patients having bilateral renal involvement with nearly universal fatal outcome. Hence an early diagnosis is very important with awareness of its manifestations, imaging and renal histology. Appropriate antifungal therapy with nephrectomy can save many patients with renal mucormycosis.

Author's contributions

Main draft and editing by KLG. Critical revision for important intellectual content by AG.

Conflict of interest

The author declared no competing interests.

Funding/Support

None declared.

Acknowledgments

None declared.

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