

Multiple Myeloma and Acute Kidney Injury: Mechanisms Involved

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ABSTRACT

The renal manifestations of multiple myeloma are devastating coupled with a disease as aggressive as the aforementioned. Its pathophysiological understanding has been clarified over time and has revealed the different mechanisms by which difficult-to-manage kidney damage occurs. However, the different therapies that have been developed have made this disease have an increasingly better prognosis. It is still a therapeutic challenge to treat myeloma together with a disease as complex as kidney disease.

ARTICLE DETAILS

Published On:
25 October 2022

Available on:
<https://ijmscr.org/>

INTRODUCTION

Multiple myeloma (MM) is a plasma cell disorder characterized by the abnormal proliferation of malignant-type plasma cells that produce monoclonal proteins and cause damage to various organs. The involvement of the kidney in plasma cell dyscrasias, including multiple myeloma, is very clear, however the mechanisms of kidney injury are not well described. Kidney disease is quite common, even called "myeloma kidney." At the time of diagnosis, about 50% of patients have some degree of kidney involvement, which is associated with higher mortality, both due to the lymphoma itself and kidney disorders.^{1,2}

It can be divided into the following 3 presentations:

Plasma cell dyscrasia: a group of manifestations characterized by the abnormal proliferation of the same type of cell lineage of plasmatic origin that can also secrete a monoclonal immunoglobulin and in turn an immunoglobulin fragment.³

Solitary plasmacytoma: An early-stage plasma cell dyscrasia characterized by single lesions in bone or (in rare cases, soft tissue) known as solitary extramedullary plasmacytoma.³

Multiple Myeloma: A malignant plasma cell dyscrasia characterized by uncontrolled proliferation of plasma cells of monoclonal origin in the bone marrow.³

Monoclonal gammopathies are caused by the proliferation of plasma cells in the bone marrow and causing deposits of immunoglobulins to be deposited in the tissues. Kidney injury

is one of the earliest signs in multiple myeloma and even in light chain amyloidosis. Despite the development of new screening and diagnostic systems for myeloma, the general prognosis (and renal function in particular) remains poor.^{4,5} Kidney injury can be classified into three large groups, those mediated by immunoglobulin, those not mediated by immunoglobulin mediated by immunoglobulin, and glomerulonephritis. The most common has been identified as the one that is mediated by immunoglobulin, also known as a cylindrome-mediated nephropathy or "renal myeloma" which has deposits of monoclonal immunoglobulins and light chain amyloidosis. This lesion, so characteristic of myeloma, includes hypercalcemia, tumor lysis, low renal volume, nephrotoxicity due to the drugs used, among many others.^{6,7} Glomerulonephritis can present itself in various forms, from proliferative to cryoglobulinemia and even, in the worst cases, membranous or minimal changes.⁸

PATHOPHYSIOLOGY

Renal involvement has been extensively studied in patients who have had alterations in plasma cells caused by myeloma, such as glomerulonephritis that is dependent on immunoglobulin. Renal injury will depend on the amount of light chains present in the urine. Something curious must be taken into consideration, not necessarily all light chains cause kidney damage, since their composition consists of amino acids with different electrical charges that make them

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different. The risk of light chain precipitation exists when the pH of the solution reaches the pH of the light chain amino acids. There are multiple risk factors that can predispose to kidney injury in this type of patient, they share certain similarities with patients with chronic kidney disease. Some of these are the use of non-steroidal anti-inflammatory drugs, hypercalcemia, hyperuricemia as well as the administration of contrast media.^{9,10}

Speaking of immunohistochemistry, it has been described that cast nephropathy is the most prevalent cause in multiple myeloma, followed by hypercalcemia induced by bone cell lysis. The light chains that have been generated are taken up by the glomeruli and are analyzed by the cubulin and megalin receptors. When the number of light chains increases and these exceed the receptors' uptake and processing capacities, it results in an increase in concentrations in the renal tubules, thus generating an accumulation of these.^{10,11}

These chains are not very susceptible to degradation, so they produce a proinflammatory state that in turn induces the release of oxygen radicals that begin to generate kidney damage originating in the kidney tubules and leading to apoptosis. Once the concentrations increase and reach the distal tubules, a union is made between the uromodulin and the Tamm-Horsfall protein to form the so-called myeloma cylinders, these cause a significant flow obstruction and atrophy of the proximal tubules as well as fibrosis. In summary, the pathophysiology of renal dysfunction can be explained by fibrosis in the renal tissue.^{11,12,13}

Due to the ability of light chains to form cylinders once they are filtered, they can cause overdilatation in the distal tubules and, in severe cases, rupture them. The given interaction between the light chains and other involved proteins results in what is known as beta pleated sheets, which are involved in the production of amyloidosis. Immunoglobulin-mediated vascular disease can result in endothelial damage, making the plasma more viscous, causing type A Immunoglobulin deposition, causing Henoch Schölein purpura, and even Immunoglobulin nephropathy.¹³

EVALUATION OF KIDNEY DAMAGE

The diagnosis and evaluation of kidney damage in a patient diagnosed with multiple myeloma must be done correctly because the prognosis is poor without adequate and timely treatment. Several studies have evaluated that CKD-EPI that in turn uses cystatin C not only predicts survival, but can also evaluate more patients with multiple myeloma and kidney injury. Several parameters are taken into account to diagnose kidney injury, including a creatinine of more than 2mg/dL, serum calcium greater than 12mg/dL (due to the high rate of bone destruction), hemoglobin less than 10g/dL, presence of paraproteins can be an indication of kidney injury but they cannot always be reliably detected.^{14,15}

Additional tests for abnormal myeloma proteins may be done using sulfosalicylic acid. Proteins in 24 hours and creatinine would be abnormal due to the presence of paraproteins, this

should be suspected when the creatinine/microalbumin ratio is low and the protein/creatinine ratio is high. Paraproteins should be suspected when the ratio of urine microalbumin to urine creatinine is low and the ratio of urine protein to urine creatinine is high. Serum protein electrophoresis (SPEP) is not highly recommended for staging light chain counts as it cannot differentiate between monoclonal and polyclonal chains. Other studies evaluate that serum immunofixation (SIFE) has a very limited use to monitor the progress as well as to evaluate the response to myeloma treatment.^{14,15}

TREATMENT

First-line treatment should focus on evaluating the stage of renal failure and correcting the uneven states of plasma volume as well as the hydroelectrolytic disorders present. In addition, once the pathology has been identified, the formation of cylinders and paraproteins should be reduced as much as possible. Most people reduce kidney damage to a greater or lesser extent by treating myeloma.^{14,15,16}

Nephrotoxic drugs such as NSAIDs, ACE inhibitors, contrast studies and hypotension that may occur should be avoided at all costs in order to avoid prerenal injury. Depending on the degree of renal insufficiency, hemodialysis may be required to relieve uremic symptoms and help control electrolytes. It has been shown that the use of dialysis for prolonged sessions can help eliminate light chains and recover renal function.^{14,15,16}

The concentration of the proteins present can be lowered by the use of chemotherapy, or in select cases, plasmapheresis. The use of bisphosphonates has been proven to reduce the risk of hypercalcemia events. The most widely used agents are pamidronate, which has shown very high efficacy.^{14,15,16}

In the event that a patient with multiple myeloma requires a contrast study, the risk can be measured with the levels of beta-2-microglobulin, if it is less than 2.8 mg/dl they are within safe ranges. Renal transplantation may be considered if the myeloma is in remission for at least 3 years, however the rejection rate is high and is associated with the use of immunosuppressants as well as myeloma recurrence.¹⁶

CONCLUSIONS

Multiple myeloma is undoubtedly an extremely aggressive and complex pathology in terms of the oncological syndromes it develops. The role of renal fibrosis, together with the amount of accumulation of light chains in renal cells, makes treatment complex. Although the evidence shows that it can be treated like a common kidney disease, the fact that it is refractory and the little degradation of myeloma cylinders make it more aggressive and rapidly progressive. The correct management, early diagnosis and pathophysiological understanding make the patient's prognosis better and better. The doctor must use all the therapies at his disposal to be able to carry out a management that encompasses the greatest number of affectations in the patient to be treated.

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