Paraproteinemia and Kidneys – from Henry Bence Jones till Now Days

Abbreviations: GOMMID: Glomerulonephritis with Organized Microtubular Monoclonal Immunoglobulin Deposits; PGMID: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition; IKMGRG: International Kidney and Monoclonal Gammopathy Research Group; MGUS: Monoclonal Gammopathy of Undetermined Significance; MGRS: Monoclonal Gammopathy of Renal Significance;

Editorial

London, November 1845. Dr William MacIntyre and Dr Thomas Watson, taking care of a patient with severe chest pain and peripheral edema, investigated his urine with unusual properties - patient noticed that his «body linen was stiffened by his urine". They sent the urine sample to Dr Henry Bence Jones with the note: "Dear Dr Jones, [...] the tube contains urine of very high specific gravity. When boiled, it becomes slightly opaque. On addition of nitric acid, it effervesces, assumes a reddish hue, and becomes quite clear, but as it cools, assumes the consistency and appearance which you see. Heat reliquifies it. What is it?" Dr Henry Bence Jones tested the urine sample himself and presumed that the substance, defining unusual properties is "deutoxide of albumin". Now we know that it was not albumin, but free light chains, and can presume that the patient suffered from multiple myeloma with cast nephropathy, which was not yet described at that time. This is in agreement with autopsy findings, revealed by Mr Shaw in January 1846. Autopsy report says: "soft and brittle ribs were noted to the extent that the osseous ribs crumbled under the heel of the scalpel". No signs of kidney amyloidosis, which was well-recognized by that time as "lardaceous changes", were found. Dr John Dalrymple, who performed histological examination, noted that mollites ossium was due to replacement of bones by a "gelatin-form substance of a blood red color and unctuous feel" and described nucleated cells which were present in large numbers in the affected bones. Illustrations from his report depict what we now days know as plasma cells.

Later on, in 1867 Herman Weber, who also worked in London, described a patient with mollites ossium and amyloidosis, who suffered from severe sternal and lumbar pain. Amyloid was found in the kidneys, and this was the first time a connection was made between amyloidosis and what we now know as myeloma, however only in 1876 Ossip Von Rustizky in Kiev first employed the term "myeloma" in describing the condition. Approximately the same time Waldeyer coined the term "plasma cell", and the term "Bence Jones protein" was first used by Dr Fleischer in Erlangen in 1880. In 1889 Otto Kahler in Vienna described a patient with bone pains (autopsy found large round cells in patient's ribs and thoracic vertebrae), anemia and proteinuria, and found that his urine protein had the same characteristics as described by Bence Jones. In 1909 Alfred von Decastello in Vienna described an association between myeloma and tubular plugging by an amorphous substance. This syndrome became known as cast nephropathy, or "myeloma kidney".

Editorial

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In 1899 A Ellinger supposed that in the blood in patients with myeloma there might be abnormal protein, similar to the Bence Jones protein in urine, and later, in 1929, a Bence Jones-like protein was detected in blood by Short and Crawford. That very year Michail Arinkin in Leningrad introduced bone marrow aspiration, which greatly facilitated the diagnosis of myeloma. In 1933 Wintrobe and Buell described the phenomenon of cryoprecipitation and supposed that the pathologic proteins in plasma cell disorders were distinct from all normal serum proteins, and in 1937 Arne Tiselius in Uppsala separated three fractions of serum globulins by electrophoresis. Two years later, in 1939, Tiselius isolated antibody activity in globulins gamma-fraction, the same year Longsworth and his colleagues first detected by electrophoresis myeloma serum "M-spike", actually representing abnormal globulins or fragments thereof, including Bence Jones protein.

In 1956 Leonard Korngold and Rose Lipari in New York identified two different classes of Bence Jones proteins designated, in their honor, as light chains kappa and lambda. In 1961, Waldenström developed the concept of clonality, thus allowing us to arrive at today's definition of Bence Jones protein as a monoclonal globulin protein found in the blood or urine. One year later, in 1962, Edelman and Gally in New York confirmed that light chains separated from serum, and urine Bence Jones protein from the same patient had identical properties. The immunoglobulin light chains precipitated at temperatures between 40°C and 60°C, and dissolved upon boiling, just as Dr Bence Jones had described [1, 2].

The harmful nature of myeloma proteins to the kidneys, beyond above mentioned cast nephropathy and amyloidosis, were also recognized. The first description of an association between myeloma and acquired Fanconi syndrome (now known as light chain tubulopathy or crystal-storing histiocytosis) came in 1963 by Constanza and Smoller. Non-amyloid glomerulopathies, including nodular glomerulosclerosis, in myeloma patients were first documented by Kobernik and Whiteside in Montreal, and in

1976 Randall from Scotland reported such changes as light chain deposition disease. Since that non-amyloidogenic light chains in myeloma are called "Randall-type". Later - in 1993 - Pierre Aucoututier and his colleagues in Poitier described also heavy chain deposition disease with the same pathology pattern [1].

There are several more rare types of paraproteinemic kidney damage. Porush and Churg with colleagues in 1969 published a paper entitled "Paraproteinemia and cryoglobulinemia associated with atypical glomerulonephritis and the nephrotic syndrome", Morel-Maroger and his colleagues in 1970 described kidney pathology in six patients Waldenström's macroglobulinemia, showing striking voluminous deposits on the endothelial aspect of the glomerular basement membrane, consisting exclusively of IgM. Schwarz and Lewis in 1981 coined the term "Immunotactoid glomerulonephritis" for glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits (GOMMID), while rapidly progressive "crescentic" glomerulonephritis in myeloma was described by Alain Meyrier in Paris in 1984. First description of proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGMID) was made by S Nasr and his colleagues from Mayo Clinic in 2004, and finally monoclonal gammopathy-associated focal and segmental glomerulosclerosis was reported by Dingly, Kyle and colleagues, also from Mayo Clinic, in 2005. Importantly, types of organized (fibrils, microtubules, casts, crystals) and non-organized paraprotein deposits, causing kidney damage, depend on intrinsic properties of misfolded pathologic immunoglobulin's or fragments thereof [3].

Even more important is that the cast nephropathy and light chain tubulopathy are characteristic for multiple myeloma; cryoglobulinemia type I-associated cryoglobulinemic glomerulonephritis as well as glomerulonephritis with monoclonal IgM deposits are typical for Waldenström's macroglobulinemia, while conditions like immunoglobulin-related amyloidosis, light/heavy chain deposition disease, GOMMID and PGMID often are seen in absence of overt lymphoproliferative disease. Thus, AL amyloidosis for many years beared a name of "primary amyloidosis", and low-grade paraproteinemia with different types of kidney lesions was described in terms like "monoclonal immunoglobulin deposition disease with monoclonal gammopathy of undetermined significance" or "glomerulonephritis with monoclonal gammopathy of undetermined significance". That was the case despite the concept of dangerous small B-cell clones, introduced by J Merlini and MJ Stone in 2006 postulated that small clone can synthesize a very toxic protein, producing devastating systemic damage and protean clinical presentations, while the monoclonal protein can aggregate and deposit systemically as occurs in light-chain amyloidosis, monoclonal immunoglobulin deposition disease, crystal-storing histiocytosis, and monoclonal cryoglobulinemia [4].

Only in 2012 International Kidney and Monoclonal Gammopathy Research Group (IKMGRG) released a paper, which synthesized the data concerning renal consequences of low-grade paraproteinemias, or monoclonal gammopathy of undetermined significance (MGUS), and the term "monoclonal gammopathy of renal significance" (MGRS) was proposed in order to discriminate the pathologic nature of these diseases from the truly benign MGUS. The main message of this really outstanding publication was as follows: "multiple myeloma is the most frequent monoclonal gammopathy to involve the kidney; however, a growing number of kidney diseases associated with other monoclonal gammopathies are being recognized. Although many histopathologic patterns exist, they are all distinguished by the monoclonal immunoglobulin (or component) deposits. The hematologic disorder in these patients is more consistent with MGUS than with multiple myeloma. Unfortunately, due to the limitations of the current diagnostic schema, they are frequently diagnosed as MGUS [...]. There is a need for a term that properly conveys the pathologic nature of these diseases. We think the term monoclonal gammopathy of renal significance (MGRS) is most helpful to indicate a causal relationship between the monoclonal gammopathy and the renal damage and because the significance of the monoclonal gammopathy is no longer indetermined" [5].

New York, April 2015. In the program manuscript, published in the Kidney International Journal, IKMGRG postulated: "MGRS regroups all renal disorders caused by a monoclonal immunoglobulin, secreted by a nonmalignant B-cell clone. By definition, patients with MGRS do not meet the criteria for overt multiple myeloma/B-cell proliferation, and the hematologic disorder is generally consistent with monoclonal gammopathy of undetermined significance (MGUS). The spectrum of renal diseases in MGRS is wide, including old entities such as AL amyloidosis and newly described lesions, particularly proliferative glomerulonephritis with monoclonal Ig deposits and C3 glomerulopathy with monoclonal gammopathy. Kidney biopsy is indicated in most cases to determine the exact lesion associated with MGRS and evaluate its severity. Diagnosis requires integration of morphologic alterations by light microscopy, immunofluorescence and electron microscopy [...]. Complete hematologic workup [...] is required" [6].

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