ASPECTS OF CHRONIC RENAL DISEASE IN CHRONIC LEUKAEMIAS

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SUMMARY: Haemato-oncological diseases (leucosis, multiple myeloma etc.) are one of the causes inducing renal disease, either as a result of direct invasion, or following organic modifications induced by the basic malignancy and/or by the therapies administered. Among these, chronic leukaemia holds a key role, due to the high incidence of hyperuricemia, hypercalcemia and lysosymuria, renal infiltration with specific cells or association with risk factors, co-existing pathology, infectious factor or anti-neoplastic treatment with nephrotoxical potential. The goal of this study is to evaluate the incidence of renal disease in patients diagnosed with haemato-oncological conditions of the type of chronic leukaemia, and the differences identified between different types of such diseases (myelocytic or lymphocytic). In order to produce this retrospective study, we processed the data of 306 patients with chronic leukaemia, admitted to the Haematology Clinic of the Timisoara Municipal Hospital between January 2002 – March 2009, divided in two lots, depending on the type of chronic leukaemia identified. Incidence of renal impairment at the onset of the haematological disease registered similar values (9.45% in the case of the CML lot vs 9.91% in the CLL lot), while after the onset of the malignant haemopathy, the incidence of chronic renal disease registered values in a close range (6.75% in the first lot vs 5.6% in the second lot); in exchange, statistically significant differences were identified between the two lots in terms of co-existing pathologies (32.43% vs 54.74%) and risk factors such as hyperuricemia (100% vs 39.13%), proteinuria (57.14% vs 43.47%) and anaemic syndrome (100% vs 50%). In conclusion, hyperuricemia, proteinuria and anaemia developed during the haemato-oncological disease are other risk factors that have a similar role to co-existing pathologies (HBP, obstructive factor, infectious complications) in triggering renal disease. Overall, the chronic renal disease was present in similar percent values in the two lots of chronic leukaemia patients (16.21% vs 15.51%), significantly higher compared to renal disease rates in the general population.

Key Words: chronic renal disease, chronic leukaemia, hyperuricemia, cytostatics

ASPECTE ALE BOLII CRONICE DE RINICHI CU LEUCEMIILE CRONICE

Rezumat: Bolile hemato-oncologice (leucozele, mielomul multiplu, etc) reprezinta una din cauzele de afectare renala fie ca urmare a invaziei directe, fie in urma modificarilor organice induse de afectiunea maligna de baza si/sau curelor terapeutice administrate. Dintre acestea leucemile cronice ocup a un rol principal, datorita incidentei ridicate a hiperuricemiei, hypercalcemiei si lizozimurii, infiltrarilor renale cu celule specifice sau asocierii factorilor de risc, a comorbidiitatelor, factorului infectios sau chimioterapiei cu potential nefrotoxic. Obiectivul acestui studiu este acela de a evalua incidenta aparitiei afectarii renale la pacientii diagnosticati cu afectiuni hemato-oncologice de tipul leucemilor cronice si a diferentelor identificate intre tipul acestora (mielocitara vs limfocitara). Pentru realizarea acestui studiu retrospectiv au fost prelucrate datele unui numar de 306 de pacienti cu leucemii cronice internati in perioada ianuarie 2002 – martie 2009 in Clinica de Hematologie a Spitalului Municipal Timisoara impartiti in doua loturi in functie de tipul leucemiei cronice identificata.

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INTRODUCTION

Renal disease is one of the complications noticed in neoplastic processes.

Malignant haemopathies may affect the kidney. Kidney pathology most frequently appears with the Hodgkin syndrome and the multiple myeloma. It is also described during chronic lymphatic leukaemia. It is seen less frequently with other malignant haematological diseases: Waldenstrom’s macroglobulinemia, chronic myeloid leukaemia.

There are many different ways in which haematological diseases can affect the kidney: glomerulonephritis related to the basic disease, tubular-interstitial pathology, urinary obstructions, amyloidosis. The kidney is also affected in hydro-electrolytic disruptions, hyperuricemia, hypercalcaemia, cryoglobulinemia. In myeloid leukaemia, especially monocye leukaemia, tubular defects may co-exist, leading to potassium and magnesium losses. Renal impairment is even more present when there is an existing basic renal disease.

A number of studies (3-10) have pointed out that haematono-ontological disease can produce renal disease through various mechanisms. Thus, chronic renal disease can appear either as a result of direct invasion, or following organic modifications induced by the basic malignancy and/or the therapies administered.

One role in inducing renal lesions in malignant haemopathies is ascribed to the infiltration of the kidney with the excess of cells produced. Kidney infiltration is rare and of a focal character. GT Robinson et al described a case of chronic renal failure in a CML patient with a biopsy indicating infiltration of kidneys with cells similar to blood and bone marrow cells.(3) In cases of LLC, functional kidney impairment is described, in relation to lymphocyte infiltration at kidney level. (11, 31).

Rifkin records a case of CLL with secondary renal failure subsequent to a dense interstitial infiltration. (12)

According to a study conducted by AC Ferreira et al, the speciality literature only describes 11 cases of chronic renal failure associated with chronic lymphatic leukaemia induced by kidney infiltration with specific cells. Although this infiltration is seen in 63-90% of the CLL cases (proven by autopsy), chronic renal disease is very rarely determined directly. Most cases of renal failure usually occur from association of risk factors, co-existing pathologies, infectious factor and neoplastic treatment. (4-11, 13) As a matter of fact, it is deemed that leukemic infiltration of kidneys is an extremely rare cause of chronic renal failure.(13)

On the other hand, immune suppression subsequent to cytostatic treatment is a major favouring factor to developing infectious complications and episodes of acute renal failure that can lead to development of chronic renal disease. (1)

Chemotherapy may have a nephrotoxic effect. The drugs used in treating malignant haemopathies have toxic potential. They can affect specific organs, as well as the body as a whole. The kidney, with rich circulation and a role in eliminating the drugs and their metabolites, accounts for one of the organs with highest exposure to drug toxicity. (14) Antineoplastic treatment can be nephrotoxic and lead to renal failure through impairment at tissue, interstitial and rarely glomerular level, as well as through mechanisms affecting renal circulation. There are two main mechanisms for eliminating drugs and their metabolites at kidney level: glomerular filtration and tubular secretion. One major current concern is the presence of renal failure in patients with neoplasies that require cytostatic therapy, with the risk for systemic toxicity and the elimination of drugs greatly delayed, especially that there are drugs with excretion mechanisms that are yet to be known. (15-19) Presence of chronic renal disease in a patient with malignant haemopahcy can favour the toxic action of cytostatic medication. Two cases of membrane glomerulonephritides have been described in the literature, with histological confirmation in patients with chronic myeloid leukaemia.
presenting severe renal complications, of the type of significant nephrotic syndrome with massive proteinuria, who developed acute renal failure under cytostatic therapy, which led to an aggravation of the pre-existing renal disease. (2)

Many authors have reported occurrence of chronic renal disease in patients with chronic leukaemia under cytostatic treatment. Thus, it was noticed that, in chronic myeloid leukaemia treated with alpha-interferon, renal lesions may occur, expressed in focal and segmental glomerulonephritis accompanied by renal failure. (20, 21). Part of the complications of the interferon therapy are dealt with by the immune system, with antibodies being formed. (22) Sporadically, renal failure was noticed following treatment with large doses of imatinib-mesylate (gleevec) in the blastic phase of CML. (23-25) In some rare cases, fludarabine used in treating chronic lymphatic leukaemia induces lesions at glomerular level, of the type of mesangio-capillary glomerulonephritis. (26, 27). As a matter of fact, renal failure is rarely noticed during cytostatic treatment. In a study conducted by Holowiecki on 34 AML patients who had been given DAF cytostatics (daunorubicin, cytarabine and fludarabine), no case of renal failure has been reported. (28)

It is clear from the above that occurrence of renal disease in malignant haemopathies includes a great number of factors. As a consequence, an acute disease may occur, such as acute renal failure, or a chronic disease, leading to a chronic kidney disease. This is frequently associated with glomerular impairment.

As a matter of fact, glomerulonephritis is perceived as a rare complication of malignant haemopathies. Most frequently, it is associated with the Hodgkin disease, followed by non-Hodgkin lymphoma and chronic myeloid leukaemia. (29)

Chronic lymphatic leukaemia is a malignant haemopathy reported relatively frequently. Renal lesions, however, are rarely noticed. Most frequently, it is associated with the nephrotic syndrome. (30, 31) Some cases co-exist with a renal functional impairment. (31) The renal lesion most frequently manifests as mesangio-capillary glomerulonephritis. Other forms of manifestation noticed were minimum lesions, membrane nephropathy, focal glomerulonephritis.

Mesangio-capillary glomerulonephritis is accompanied by the presence of serum cryoglobulins. Viral infection with the hepatitis C virus may co-exist. In this morpho-pathological form, however, immuno-fluorescence tests have identified deposits of IgG and IgM in the kidney. In some cases of mesangio-capillary glomerulonephritis, cryoglobulins are not present in the serum. (31, 32)

Mesangio-capillary glomerulonephritis in CLL has been reported to improve under cytostatic and prednisolon treatment. (31) Sometimes the cytostatic treatment leads to remission of the CLL, but the prednisolon was needed to get remission of the nephrotic syndrome. (33) Halimi et al. report a case of CLL with nephrotic syndrome resistant to immune suppressants, but gone into remission after splenectomy. (34) CLL can be accompanied by amyloidosis. It has been noticed in case of hairy cell leukaemia. (35) Chronic myeloid leukaemia rarely associates with glomerular lesions. There is description of one case of CML complicated with nephrotic syndrome with minimal lesions. (36)

This work aims at analysing chronic renal impairment in chronic leukaemia. Since the factors mentioned above are active for a long duration of time, they induce chronic renal lesions, accompanied or not by renal functional impairment. The chronic renal disease within chronic leukaemia was defined according to the guide developed by The Kidney Disease Outcomes Quality Initiative (K/DOQI). We will also mention that we considered evaluation of the renal impairment over a period of at least 3 months, with RFG<60 ml/min/1.73m² in presence or absence of renal lesions. (38, 39)

Therefore, the study tackles on the incidence of chronic renal disease in chronic leukaemia based on the case files of a haematology clinic of wide addressability: the Haematology Clinic of the “Victor Babes” Medicine and Pharmacy University in Timisoara. The data were compared with the data existing in the speciality literature, proven by numerous studies that mainly looked at the incidence of chronic renal disease in the general population. Such studies took a wide range of factors into account: age, gender, ethnicity, as well as risk factors to the chronic renal disease. In average, the kidney disease rate is 7.2% in the world (ranging between 1.5% and 43.3%, depending on the study) in the 30+ population group. The NHANES Study (National Health And Nutrition Examination Survey) estimated that 4.7% of the adult population in the US shows RFG <60ml/min/1.73mp. (40-44)

**MATERIALS AND METHOD**

The goal of this study is to evaluate the chronic renal disease in patients with known chronic leukaemia under cytostatic treatment in various therapy schemes. Following retrospective analysis, a number of 306 patients were identified with chronic leukaemia,
admitted at the Haematology Clinic of the Timisoara Municipal Hospital over the course of seven years, namely between January 2002 – March 2009, undergoing various schemes of cytostatic treatment.

Depending on the type of haematological disease – lymphatic or myeloid – the patients were divided into two lots. Thus, the first lot included 74 patients diagnosed with forms of chronic myeloid leukaemia (CML), while the second lot included the remaining 232 patients diagnosed with chronic lymphatic leukaemia (CLL). We will also mention that the second lot included 7 patients with hairy cell leukaemia, as this is a form of chronic leukaemia with monoclonal proliferation, originating from B lymphocytes.

Within the period mentioned, the patients were watched dynamically, with each having at least 4 hospital admissions. In order to establish the degree of renal impairment, anthropometrical indexes were monitored, as well as blood biology parameters (urea, creatinine, uric acid) and urine parameters (urine test, proteinuria, uroculture), alongside para-clinical investigations (EKG chart, lung X-ray, abdominal echograph tests). Proteinuria was determined using dipsticks. Glomerular filtration rate was calculated depending on the four variables: age, gender, race, value of blood creatinine rate, according to the formula in the guide developed by The Kidney Disease Outcomes Quality Initiative (K/DOQI).

At the same time, we looked at the presence of chronic kidney disease risk factors: senescence, anaemic syndrome, HBP, diabetes mellitus, hyperuricemia, recurring urinary infections, other co-existing malignancies, cytostatic treatment and corticotherapy.

RESULTS

The first lot (CML) including patients diagnosed with chronic myeloid leukaemia had the following gender and age distribution: 41 patients were male (55.4%) aged between 29-83 years (the average age being 51.85±13.33 years old) and 33 were female (44.6%) aged between 26-80 years (the average age being 52.82±12.62 years old).

32.43% (24 cases) initially had various co-existing pathologies: 6 patients had diabetes mellitus, 10 patients had high blood pressure, one case had HBP associated with diabetes mellitus, and one case was diagnosed as hypertensive with polycystic kidney. Hyperuricemia was present at the onset of the haematological disease in 18 patients (24.32%) out of which 8 were women (uric acid >6 mg%) and 10 were men (uric acid >7 mg%). Proteinuria showed in 7 patients (9.45% of cases), with 4 of them being known with chronic renal failure at the time of registration for the haematological pathology.

As for the chronic renal disease, the majority of patients had not been diagnosed with a pre-existing renal impairment, with only 7 cases (9.45%) having RFG <60ml/min/1.73mp, 6 of the patients being stage III chronic renal disease and one patient stage IV. All these patients were aged 50+, with four of them hypertensive and one known with polycystic kidney. Hyperuricemia showed in all patients with chronic renal disease, and proteinuria in 57.14% of cases. During the period monitored, none of these patients modified their stage of chronic renal disease, although 2 of them did show repeated infectious complications, which led to increased nitric retention with acute episodes of the renal failure, which went into remission after initiation of antibiotics treatment.

Only 5 patients with CML under chemotherapy (6.75% of cases), who at the onset of the haematological disease had normal renal function and RFG >60ml/min/1.73mp, developed renal chronic disease over the period monitored. Evaluation of the presence of risk factors in these patients, as well as of the infectious complications they had developed and the chemotherapy scheme applied, has revealed the following: anaemic syndrome was present in 100% of the cases; only one female patient was hypertensive; one case had co-existing hyperuricemia and proteinuria after having developed the chronic renal disease; two patients (40%) had infectious complications other than renal, which resulted in urea and creatinine values increasing above normal, but with the renal function coming back to normal under antibiotic treatment. 4 patients (80%) were under treatment with hydroxy-urea and one was under treatment with imatinib-mesylate. We should mention that this latter patient, aged 37, did not show chronic renal disease risk factors, except for a mild anaemic syndrome, but he was under chronic Gleevec (imatinib-mesylate) treatment and, during acute periods of the haematological disease, he was placed under more aggressive therapy schemes with cytosine-arabinoside and idarubicinum.

The second lot (CLL) included patients with chronic lymphatic leukaemia and had the following distribution in terms of gender and age: 132 patients were male (56.9%) aged 30-86 years (the average age being 64.29±10.86 years old) and 100 were female (43.1%)
aged between 39-88 years (average age $64.27 \pm 11.18$ years old).

Among them, a percent significantly higher than in the first lot – 54.74% - had co-existing pathologies (127 patients), namely: 61 patients were hypertensive; 10 had diabetes; 10 cases had diabetes associated with HBP; 10 hypertensive males had an obstructive factor present – prostate adenoma; 9 cases were only known with prostate adenoma, and the others had either another co-existing malignant neoplasys, or a co-existing viral hepatitis. Hyperuricemia was present at the onset of the haematological disease in 32 patients (13.79%), out of which 18 were women and 14 were men. Proteinuria was identified in 15.94% of cases (37 patients) at the moment of diagnosing the haematological disease, out of which 10 were known with chronic renal disease, with RFG $<60\, \text{ml/min/1.73mp}$, while 6 patients developed chronic renal disease over the monitored period. Proteinuria was inconsistent in the other patients.

9.91% of cases (23 patients) had kidney impairment at the onset of the haematological disease; they were all aged 50+; 5 were hypertensive, 2 with diabetes, 3 had HBP associated with diabetes mellitus, and 13.04% showed co-existing prostate adenoma. Unlike the first lot, where hyperuricemia was present in all cases, in the second lot it was present in 39.13% of cases (9 patients), while proteinuria was present in 43.47% (10 patients). In terms of staging of the chronic renal disease, the majority (22 cases) had RFG between 30-60\,\text{ml/min/1.73mp}, ranging at stage III of the disease, and one case was stage IV chronic renal disease. In terms of dynamics, these patients had not modified their chronic renal disease stage, with all overlapping infectious complications, except for one case only: an elder female patient with anaemia, diabetes and high blood pressure, with recurrent urinary infectious episodes, under treatment with chlorambucil, whose renal disease advanced from stage III to stage IV.

During the period monitored, chronic renal disease appeared in a number of 13 patients (5.6% cases). Anaemic syndrome was seen in approximately half of these patients (46.15%), same as proteinuria. One thing worth noticing is that none of the 13 patients showed prior hyperuricemia, and only 2 patients were hypertensive, with one of them having an obstructive factor present as well. Infectious complications such as recurrent urinary tract infections with significant bacteriuria ($>100,000$ colonies/ml) and positive urocultures occurred in 4 of these patients (30.76% cases), which led to urea and creatinine values increasing over the higher normal limits. As for the cytostatic treatments applied, the majority of patients (10 patients – 76.92%) were undergoing CVP chemotherapy (cyclophosphamide, vincristin and prednison), one CHOP (cyclophosphamide, doxorubicin, vincristin and prednison), one patient was treated with chlorambucil and one treated with fludarabine.

One thing we noticed in our study was that none of the 6 patients diagnosed with hairy cell leukaemia and having good renal function, undergoing alpha-interferon treatment, has developed chronic renal disease; as for the patient known with chronic renal failure, no aggravation of renal pathology has been noticed.

DISCUSSIONS

- The chronic renal disease was reported in relatively similar rates in both lots at the onset of the malignant haemopathy (9.45% in the CML lot vs 9.91% in the CLL lot) ($p=0.90888$ n.s) (fig. 1)
Except for one case with cumulated risk factors, none of the patients in the two lots, identified with renal impairment (RFG<60 ml/min/1.73 mp in stage III and IV) prior to the haematological disease showed subsequent aggravation of the kidney pathology. However, statistically significant differences were reported in terms of the incidence of hyperuricemia (100% vs 39.13%) and proteinuria (57.14% vs 43.47%) during progress of the haematological disease. (fig 2, 3)

In the patients included in the study, the chronic renal disease occurred in 6.75% of the CML patients
with prior good renal function, respectively in 5.6% of the CLL patients. (fig.4)

- For these cases, we deemed it opportune to look deeper into the risk factors of the chronic kidney disease (both initiation and evolution factors). Except for one case, all patients were aged 50+. In terms of co-existing pathologies associated as risk factors in occurrence of chronic renal disease (HBP, diabetes mellitus, polycystic kidney, prostate adenoma), it was noticed that these were present in 32.43% of the cases in the first lot and 54.74% in the second lot. (fig. 5)

- Unlike the first lot, where the anaemic syndrome was present in 100% of cases, the syndrome was seen in only approximately half of the patients in the chronic lymphatic leukaemia lot.

- Infectious complications (both urinary and others) with direct effect on the renal function by development of acute renal failure episodes, subsequently gone into remission following adequate therapeutic behaviour, have been quite significant. The rate was 40% in the first lot and 30.76% in the second lot. (fig. 6)

- The diseases associated to haematological pathology were less frequent: HBP in 20%, respectively 15.38%; only one CLL patient was diagnosed with prostate adenoma (7.69%), while diabetes mellitus was not found among conditions co-existing in patients who developed chronic renal disease.

- No case of chronic glomerulonephritis or nephrotic syndrome was diagnosed in the studied lot.

- Incidence rates of the chronic renal disease were similar in the two lots along the approximately 7 years of the studied period: in the lot of CML patients, renal impairment was found in 12 patients in total (16.21%), while in the second lot, the percent was 15.51% (36 patients). (fig. 7)
We noticed from the above that, in malignant haematological diseases, kidneys are directly affected to a smaller extent (13), while they are affected especially by the contribution of a number of associated factors: existence of anaemia, proteinuria, hyperuricemia, co-existing pathologies (especially HBP and obstructive factor), infectious complications affecting the renal function, plus anti-neoplastic therapy. It is known that such therapy has a nephro-toxic potential, proven by the numerous studies conducted and mentioned in the literature quoted by many authors specialising in the field. (15-19)

Contrary to a number of studies pointing out renal impairment induced by alpha-interferon through various mechanisms (20-22), we have not come across such cases in our case files; no patient with hairy cell leukaemia and good renal function developed chronic renal disease, and if such disease existed at the onset of the haematological disease, it has not been aggravated by the interferon.

Compared to the incidence rates of chronic renal disease at the level of the general population, proven through a number of studies focused on this aspect (40-44), the percent of renal impairment in haemat-oncological patterns is significantly higher and is due to a number of cumulated factors that induce or favour the occurrence of chronic renal disease.

In conclusion, malignant hemopathies are one of the causes of renal impairment, either as a result of direct invasion, or following the organic modifications induced by the basic malignant condition and/or the treatments administered. Among these, chronic leukaemia takes a key role, due to the high incidence of hyperuricemia, proteinuria and hypercalcaemia, renal infiltration with specific cells or association of risk factors, co-existing pathologies, infectious factor within an immune-depressive pattern, and chemotherapy with nephrotoxic potential.

REFERENCES
REFERENCES (CONTINUED)

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