



Review Article

Heavy-Chain Diseases and Myeloma-Associated Fanconi Syndrome: an Update

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Abstract. The heavy chain diseases (HCDs) are rare B-cell malignancies characterized by the production of a monoclonal immunoglobulin heavy chain without an associated light chain. There are three types of HCD, defined by the class of immunoglobulin heavy chain produced: IgA (α -HCD), IgG (γ -HCD), and IgM (μ -HCD). Alpha-HCD is the most common and usually occurs as intestinal malabsorption in a young adult from a country of the Mediterranean area. Gamma- and μ -HCDs are rarer and associated with a B-cell non-Hodgkin lymphoma that produces an abnormal Ig heavy chain. These patients may occasionally be diagnosed with a monoclonal gammopathy of undetermined significance (MGUS). Fanconi syndrome, on the other hand, can be primary (inherited) or secondary (acquired). The only exception to this rule is the idiopathic form. Adult acquired Fanconi syndrome can be a rare complication of a monoclonal gammopathy. At diagnosis, most patients have an MGUS or smoldering multiple myeloma, with renal failure and evidence of osteomalacia. During follow-up, patients can develop an end-stage renal disease. Chemotherapy provides little benefit on renal function.

Keywords: B-cell malignancies, Fanconi syndrome, Heavy chain disease, Monoclonal gammopathy, Multiple myeloma.

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Introduction. Heavy chain diseases (HCDs) are a group of three rare B-cell neoplasms that are clinically and morphologically distinct from one another, but have in common the production of an abnormal immunoglobulin (Ig) heavy chain incapable of binding light chains (LCs). The altered heavy chains contain deletions, insertions, and point mutations that are acquired during somatic hypermutation. These structural abnormalities typically result in loss of a large portion of the constant-1 (CH1) domain of the Ig heavy chain molecule responsible for LC binding, with different effects on the variable (V), diversity (D), and joining (J) regions.¹⁻³

In the absence of an associated LC, the CH1 domain of the regular heavy chain binds to heat-shock protein 78 (HSP78) and undergoes degradation in the cell proteasome compartment. Regular heavy chains unassociated with LCs are therefore never detected in serum or urine. In the HCDs, the altered structure of the CH1 domain prevents the heavy chain from binding both the LC and HSP78, thereby allowing it to bypass degradation by the proteasome and be secreted into the serum or urine.⁴ In addition, recent work suggests that the altered heavy chain, which forms part of the transmembrane B-cell receptor, may facilitate antigen-independent aggregation and

Table 1. Clinicopathologic features of heavy chain disease.

	Main site of involvement	Underlying disorders	Associated diseases	References
α -HCD	Gastrointestinal system; Respiratory system	Immunoproliferative small intestinal disease (IPSID) with features of MALT lymphoma	Bacteria and parasites infection of bowel	14-17
γ -HCD	Bone marrow, spleen, lymph nodes, extra-nodal sites	Lymphoplasmacytic neoplasm: - disseminated lymphoma; - localized medullary disease; - localized extramedullary disease. Autoimmune disease	Rheumatoid arthritis and less frequently other autoimmune diseases	20-22,33-35
μ -HCD	Bone marrow	Lymphoid neoplasm with features of chronic lymphocytic leukemia/small lymphocytic lymphoma	Hepato-splenomegaly, recurrent pulmonary infections, portal hypertension, systemic lupus erythematosus, diffuse large B-cell lymphoma of the breast, myelodysplastic syndrome, systemic amyloidosis	1,25,26-29

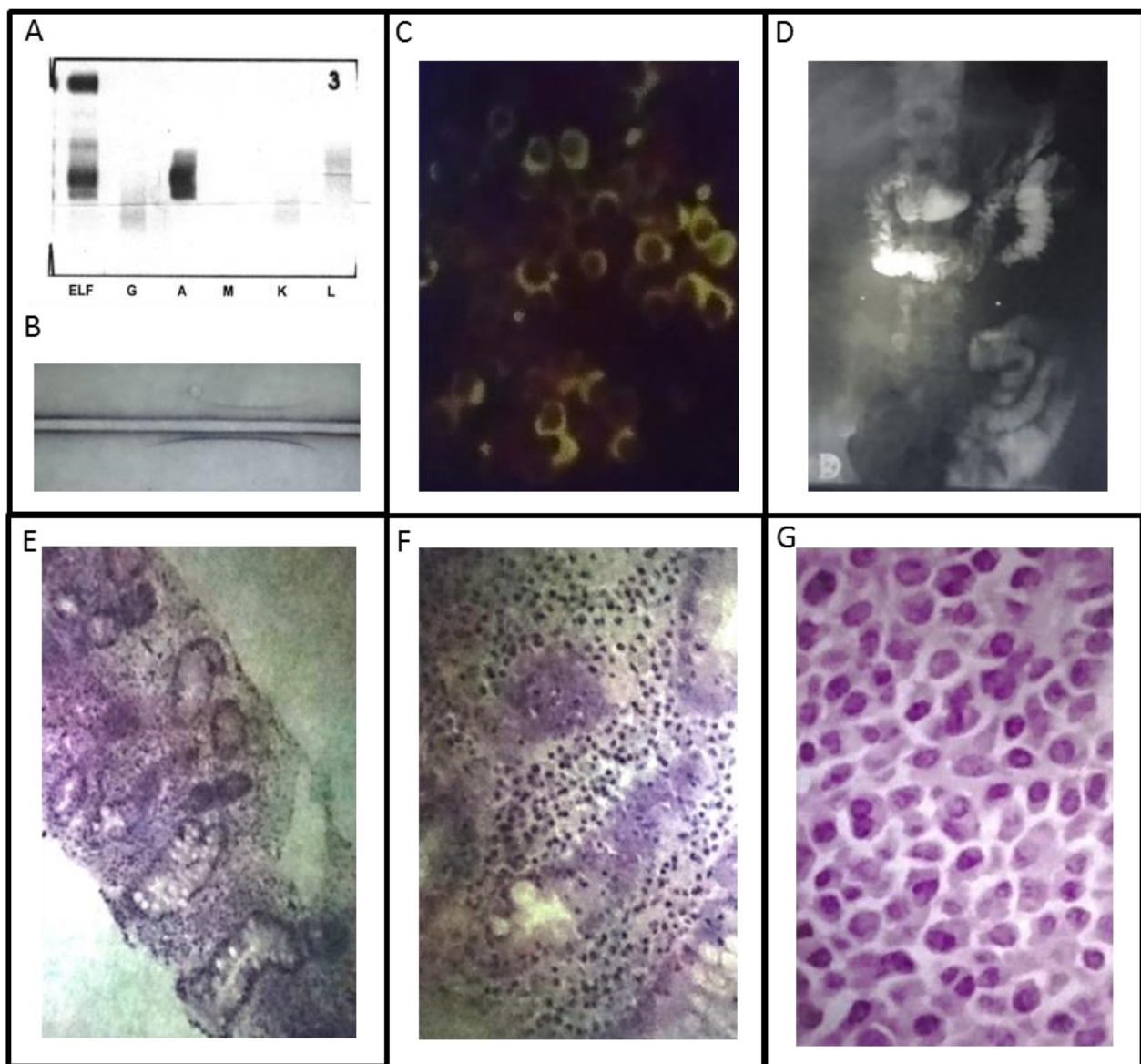


Figure 1. Clinicopathologic features in a case of IPSID with α -HCD. **A)** Immunofixation and **B)** immunoelectrophoresis positivity for the anti-IgA antiserum; **C)** plasma cells and marginal zone cells express monoclonal cytoplasmic α -chain at immunofluorescence; **D)** Radiologic studies of the gastrointestinal apparatus showing diameter alterations (dilations and strictures); **E), F)** and **G)** histological features of intestinal infiltration by α -HCD cells (10X, 20X and 100X respectively).

frequently the thyroid or parotid gland, the oropharyngeal cavity, and the gastrointestinal tract.^{20,22} Finally, 10-17% of patients have a pre-existing autoimmune disease with a clinical presentation characterized by rheumatoid nodules, rashes, synovitis, and joint deformities.

μ -HCD. – It is the rarest of the HCDs, with only 30 to 40 cases reported in the literature. The first two patients were described in 1970 by Forte et al.²³ and Ballard et al.²⁴ The disease occurs predominantly in Caucasian males, with a median age of 58 years at diagnosis.¹⁴ Most patients with μ -HCD have a lymphoid neoplasm resembling chronic lymphocytic leukemia/small lymphocytic lymphoma.^{1,25}

Palpable, superficial lymphadenopathy can be identified in 40% of the patients. Splenomegaly is frequent, and hepatomegaly can be found in about 25%.¹⁴ Rare associations of μ -HCD with recurrent pulmonary infections, portal hypertension, and pancytopenia, systemic lupus erythematosus, diffuse large B-cell lymphoma of the breast as well as myelodysplastic syndrome, carpal tunnel syndrome, and systemic amyloidosis have been reported.²⁶⁻²⁹

Diagnostic Approach. The diagnosis of HCDs remains challenging due to their rarity, their variable clinical presentation, and the skill required in interpreting immunologic laboratory tests and tissue biopsies from affected patients. A close collaboration between clinicians and pathologists is usually needed. Two-dimensional immunoelectrophoresis has been shown to be a useful diagnostic tool for all three types of HCD.³⁰

α -HCD. - Common laboratory abnormalities include mild-to-moderate hypochromic anemia, deficiency of vitamins and minerals, high levels of alkaline phosphatase (the gastrointestinal isoform of the enzyme), electrolytic disorders (i.e., hypoalbuminemia, hypocalcemia, hypokalemia, and hypomagnesemia).¹⁵ Serum protein electrophoresis may appear normal or show hypogammaglobulinemia, but sometimes a broad monoclonal band migrating to the α_2 or β region of the electrophoretic pattern can be seen. Positivity for the anti-IgA antiserum by immunofixation is mandatory to confirm the diagnosis (**Figure 1** panel **A, B**).³¹ The abnormal α -heavy chains can be detected in jejunal or gastric fluids as well as in urine in only small

amounts, but Bence Jones proteinuria has never been detected.³¹

Radiologic studies of the gastrointestinal apparatus can show diameter alterations (dilations and strictures) (**Figure 1** panel **D**), hypertrophic or pseudo-polypoid mucosa, or coarse mucosal folds.

Since α -HCD typically affects the proximal small bowel at the level of the duodenum or jejunum, endoscopy is mandatory and can reveal five different patterns: *i*) infiltrative, *ii*) nodular, *iii*) ulcerations, *iv*) mosaic, *v*) isolated mucosal fold thickening. The first two patterns are most sensitive and characteristic for the diagnosis of α -HCD.³²

The histological features of α -HCD are those of an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (**Figure 1** panel **E, F, G**), also named immunoproliferative small intestinal disease (IPSID). Bacterial or parasites infection (i.e., *Campylobacter jejuni* or *Helicobacter pylori*) can be associated.³³⁻³⁵ A lymphoplasmacytic infiltrate rich in plasma cells can be detected in the lamina propria of the bowel, and lymphoepithelial lesions may also be present. The infiltrate can cause villous atrophy and is admixed with small lymphocytes, resembling marginal zone B cells.^{33,36-38} All the α -heavy chain cells (plasma cells and marginal zone cells) typically express monoclonal cytoplasmic α -chain without light chains (**Figure 1** panel **C**). The immunophenotype of α -heavy chain cells is shown in **Table 2**. Finally, the presence of intestinal bacteria and parasites should be looked for on biopsy specimens.

γ -HCD. - Laboratory evidence of autoimmune diseases or bone marrow infiltration can be detected during diagnostic procedures in patients with γ -HCD. These comprise cytopenias, in particular, normochromic normocytic anemia, Coombs-positive autoimmune hemolytic anemia, and thrombocytopenia. In some cases, monoclonal plasmacytoid lymphocytes or plasma cells are present in the circulation, as well as features of chronic lymphocytic leukemia or plasma cell leukemia.¹⁴ Serum protein electrophoresis may appear normal or show a monoclonal band migrating to the β -region of the electrophoretic pattern, where it is often concealed by other proteins. Rarely, biclonal gammopathy with an additional intact monoclonal Ig may be present.²⁰ Positivity for the anti-IgG antiserum, without

associated light chains, by immunofixation is mandatory to confirm the diagnosis.

Due to their low molecular weight and existence as dimers, the abnormal γ -heavy chains often can be detected in the urine.² Small amounts of FLCs may be excreted in urine as Bence Jones protein.³⁹ Other laboratory findings include high serum levels of IgG, with normal serum FLCs.

The pathologic heterogeneity of γ -HCD makes the histological diagnosis rather difficult. Histological findings of γ -HCD are typically associated with a lymphomatous infiltration of affected tissues such as bone marrow, spleen, lymph nodes, as well as extra-nodal sites involved in MALT lymphomas, such as skin, thyroid, salivary glands, gastrointestinal tract, and conjunctiva.^{21,22} The infiltrate is formed by a mixed population of lymphocytes, plasmacytoid lymphocytes, and plasma cells, similarly to a lymphoplasmacytic lymphoma or, in some cases, it is more polymorphous showing immunoblasts, eosinophils, and histiocytes in a variable number. Atypical Reed-Sternberg-like cells have been described, thus inducing Hodgkin lymphoma or certain types of peripheral T-cell lymphoma to be considered in a morphologic differential diagnosis.²² Less frequently, γ -HCD can be similar to B-cell neoplasms, such as MALT lymphoma, splenic marginal zone lymphoma, or other splenic small B-cell lymphomas.²¹ The association of γ -HCD with T-cell large granular lymphocytic leukemia and extranodal marginal zone lymphoma have also been reported.^{40,41}

The immunophenotype of γ -heavy chain cells is shown in **Table 2**.

μ -HCD. – Hypoproliferative anemia related to bone marrow infiltration by neoplastic cells is the most common laboratory abnormality of μ -HCD; thrombocytopenia and lymphocytosis are less common.^{27,28} Serum protein electrophoresis is generally normal or shows a rather broad monoclonal band. In a few cases, biclonal gammopathy with an additional intact monoclonal Ig may be present.¹ Immunofixation that is positive with anti- μ but not with anti-kappa or anti-lambda LCs confirms the diagnosis.⁴² Bence Jones proteinuria is frequently detected because the neoplastic cells also produce monoclonal LCs, usually of kappa type, that fail to assemble with the truncated heavy chain;^{1,24,42} however, Bence Jones proteinuria rarely causes renal complications.⁴³

Table 2: Immunophenotypic characteristics of HCD cells.

	Heavy chain	Cell phenotypes	References
α -HCD	IgA	pan-B-cell antigens+ CD138+ CD5- CD10- CD20-	22,32
γ -HCD	IgG	CD19+ CD20+ Mum1/IRF4+ CD38+ CD138+ CD5- CD10-	4,21
μ -HCD	IgM	CD19+ CD20+ CD38+ k light chain+ (rare) CD5+ (rare)	1,28,42

Bone marrow smears and touch preparations show characteristic plasma cells with prominent cytoplasmic vacuoles admixed with small, round lymphocytes.^{1,24,44,45} The immunophenotype of μ -heavy chain cells is shown in **Table 2**.

Treatment and Prognosis. No standardized therapies are available for the HCDs, because of their rarity and their clinicopathologic features characterized by association with various conditions such as infectious, autoimmune and lymphoproliferative diseases.

α -HCD. - Since it has a higher incidence in subjects of lower socio-economic status, sanitation improvement would be expected to reduce its occurrence. If untreated, α -HCD may initially progress locally, and then spread systemically. Small bowel obstruction, perforation, and intussusception that can be fatal are the dreadful local complications of enlargement of the lymphomatous tissue. Other potential causes of death are severe malnutrition and subsequent cachexia, as well as infectious complications.⁴⁶

If a bacterial or parasitic gastro-intestinal infection is documented, it should be eradicated with appropriate antimicrobial therapy. An empirically administered antibiotic treatment is often recommended even in the absence of a demonstrated infection. Metronidazole, ampicillin, or tetracycline are the antibiotics of choice for this empiric therapy. Antimicrobial treatment should be administered for a 6-months course, although an early regression or a rapid improvement of symptoms is typically observed in antibiotic-

sensitive patients. A shorter duration has been shown to cause a relapse of the disease.

Although 33-71% of patients with early-stage show clinical, laboratory, and histological remission in response to antimicrobial treatment, disease recurrences are frequent.⁴⁷ Refractory disease is treated with either total abdominal radiation or, more commonly, with doxorubicin-containing combination chemotherapy. Regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHVP (cyclophosphamide, doxorubicin, teniposide, and prednisone), or ABV (doxorubicin, bleomycin, and vinblastine) have been shown to induce better results than doxorubicin-free regimens such as COPP (cyclophosphamide, vincristine, procarbazine, and prednisolone).⁴⁸⁻⁵⁰ The complete remission rate after treatment with multi-drug chemotherapy is 64%, and 5-year overall survival is 67%.⁵¹

Surgical debulking of the tumor mass can be pursued, followed by systemic chemotherapy, but it should be limited to the management of complications.⁵² For patients with a refractory or relapsing disease, high-dose therapy with autologous hematopoietic stem cell transplantation should be considered.

γ -HCD. - Treatment of γ -HCD is typically tailored to the symptomatology of the patient and to the presence of an accompanying autoimmune disease or overt lymphoma. Chemotherapy is recommended in patients with lymphomatous dissemination or with a localized medullary disease. Chlorambucil, or melphalan and prednisone, or bortezomib and prednisone, and rituximab in CD20-positive disease are the treatment of choice for plasma cell-predominant disease. CHOP regimen (with rituximab in CD20-positive cases) shows the best results in aggressive/refractory patients. Inoue et al.⁵³ reported that the combination of fludarabine and rituximab was effective in patients with γ -HCD associated with pancytopenia.

While surgical resection or radiation therapy have been successfully employed in patients with localized extra-nodal disease,²² a 'watch and wait' strategy can be adopted in asymptomatic patients without lymphoma. When co-existing autoimmune disorders are diagnosed, they should be treated with immunosuppressive treatments according to usual guidelines. Adequate prophylaxis and surveillance for infectious complications are

critical points. Prognosis is highly variable because of the heterogeneity of γ -HCD and the lack of a standardized treatment.

Occasional spontaneous remissions have been reported in patients with no overt lymphoma, who are nonetheless expected to undergo a prolonged survival without treatment.²² A sustained, complete clinical and immunologic remission is usually achieved in patients with treated, localized lymphoma. The natural history of γ -HCD associated with systemic lymphoma may be either aggressive and rapidly progressive, and hence associated with poor prognosis, or exhibit an indolent course. In the Mayo Clinic series, median survival was 7.4 years (range, one month to more than two decades).²⁰

μ -HCD. - Only a few data have been reported about the treatment and prognosis of this disease because of its rarity. A 'watch and wait' approach is recommended in patients with detectable monoclonal μ heavy chains who are otherwise asymptomatic.⁵⁴ If and when an underlying malignancy develops, useful treatment regimens are CHOP, CVP (cyclophosphamide, vincristine, and prednisone), single-agent fludarabine or cyclophosphamide.^{14,45} Reported median overall survival is approximately two years, ranging from less than a month to over a decade. However, these data are likely underestimated, since the presence of monoclonal μ heavy chains is frequently missed on serum protein electrophoresis, especially in the absence of an associated overt lymphoma. A spontaneous remission of μ -HCD can rarely be observed.¹⁴

Myeloma-Associated Fanconi Syndrome (MAFS).

Pathophysiology. The precise pathophysiology of MAFS is still unknown. The biological and clinical features result from the impaired function of the proximal renal tubule, consequent to reabsorption of some filtered substances.^{55,56} In particular, FLCs, generally of kappa isotype, secreted by plasma cells are a major cause of MAFS or other plasma cell dyscrasias. In virtually all cases, the diagnosis of FS precedes that of the underlying hematological disorder, generally a 'smoldering' multiple myeloma.^{11,12}

FLCs slowly accumulate in the epithelial cells of the proximal tubule, forming crystals that can be demonstrated in all cases.^{11,57,58} Accumulation and crystallization take place in the lysosomes of

tubular cells and endoplasmic reticulum of plasma cells. These LCs have the highest homology with a single germline variable segment sequence: LCO2/O12 and non-polar amino acid residues exposed in the CDR1 region.⁵⁶⁻⁵⁸ This peculiar sequence is responsible for the crystallization because of the resistance of the LC variable domain to proteolysis by several enzymes such as cathepsin B^{54,55} and of the subsequent damage of the proximal tubule. The functional impairment of the proximal kidney tubule can cause aminoaciduria, glycosuria with normal glycemia, metabolic acidosis and increased clearances of uric acid and phosphate. Phosphate loss is responsible for osteomalacia, with bone pain and pseudo-fractures.^{59,60} Intracellular crystallization seems associated with the slowly proliferative character of the tumor, in that the intracellular accumulation of crystals impairs the proliferation of plasma cells, and this may be a criterion for not treating the proliferative disease.⁶¹⁻⁶²

In contrast, when the LC variable domain derives from another germline variable segment such as LCO8/O18, MAFS occurs without evidence of intracellular crystallization, even when searched for by electron microscopy.^{63,64} In this case, defects of tubular reabsorption and urine acidification are usually a consequence of the direct toxicity of FLCs on epithelial cells of the proximal tubule, in the absence of crystalline deposits.⁶⁵ Myeloma FLCs can interfere with the uptake of alanine, phosphate, and glucose.^{66,67} There has also been one report of LC-FS and nephrogenic diabetes insipidus, suggesting that resistance to antidiuretic hormone can also occur.⁶⁸ Interestingly, this patient had distal (type D), not proximal, renal tubular acidosis.

Clinical features and diagnostic approach. Clinical manifestations of MAFS include defects in sodium-coupled co-transport processes producing type II renal tubular acidosis, aminoaciduria, phosphaturia, and glycosuria. The associated multiple myeloma is often low-grade.¹¹ The offending monoclonal FLCs are usually of the kappa type and possess uncommon non-polar or hydrophobic residues in the complementarity-determining region-1 (CDR1).⁶¹ This unique proximal tubular lesion may represent a subset of gammopathy-associated crystal-storing histiocytosis, in which crystal-forming monoclonal Igs, composed of heavy chains and typically

kappa-FLC, accumulate in lysosomes of histiocytes in soft tissues, kidney, bone marrow, spleen, liver, stomach, and other organs.⁶⁹⁻⁷⁰ Involvement of the proximal tubule occurs specifically when the monoclonal FLCs are overproduced, because intact Igs are not filtered through the glomerulus.

The typical histological finding is intra-lysosomal crystalline deposits of FLCs within epithelial cells of the proximal tubule. There may be extra-renal crystal accumulation. FLCs of the VkI subgroup are most frequently found,^{61,62} although cases associated with lambda-FLCs have also been reported.⁷¹

The diagnosis of FS can be made when a patient with a monoclonal plasma cell disorder presents with hypophosphatemia, hypouricemia, aminoaciduria, phosphaturia, and glycosuria. Bence Jones proteinuria is usually present and is almost always of the kappa type. Crystal-storing histiocytosis, an intra-lysosomal accumulation of monoclonal LCs that aggregate in crystals, is observed in association with both plasma cell and lymphoid disorders.^{72,73} Although the type of LCs involved is almost exclusively kappa, there is no consistent association with a particular heavy chain. Crystals can form either in histiocytes in soft tissues or parenchymal cells in bone marrow, lymph nodes, spleen, liver, stomach, adrenal glands, proximal renal tubules, and thyroid follicles. The initial clinical presentation depends on the site of crystal formation and is, therefore, variable. Some patients present with soft tissue masses in which predominantly histiocytes, but also fibroblasts, contain crystals. The crystal formation in proximal renal tubules is the fundamental diagnostic criterion of MAFS.

The main laboratory abnormalities include aminoaciduria, renal glycosuria, hypophosphatemia, hyperchloremic metabolic acidosis, hypokalemia, proteinuria of tubular origin, and hypouricemia. The primary manifestations include osteomalacia, polyuria, chronic acidosis, and episodes of dehydration. FS frequently evolves into end-stage renal failure.

Treatment and prognosis. The prognosis in terms of survival is good in the absence of an overt malignancy. Treatment includes symptomatic measures to prevent osteomalacia by supplementation with phosphorus, calcium, and vitamin D. Chemotherapy may benefit patients

with rapidly progressive renal failure or symptomatic malignancy.

Very few series of LC-associated FS have been published, and the efficacy of the so-called novel anti-myeloma agents, such as proteasome inhibitors and immunomodulatory drugs (IMiDs), has not been evaluated. In most cases, FS appears to progress toward end-stage renal disease slowly and rarely results in symptomatic myeloma.⁷⁴ Accordingly, therapeutic decisions should take into account treatment side effects, particularly the potential risk of secondary myelodysplastic syndrome from alkylating agents.⁷⁵

All patients with an associated overt lymphoid disorder should receive appropriate chemotherapy, and treatment choices should be adapted to the degree of renal failure. In patients with stages 1 to 3 chronic kidney disease, bortezomib-based chemotherapy should be considered because of high rates of both anti-myeloma response and recovery of renal function. In addition, cyclophosphamide- or IMiDs-based regimens are good options to treat bortezomib-refractory myeloma. Bendamustine may also be used. High-dose melphalan/autologous stem cell

transplantation (HDM/ASCT) may be performed in selected non-responding patients, although the benefit of this strategy remains to be proven. In the relapsed/refractory setting, additional treatment options such as carfilzomib, pomalidomide and monoclonal antibodies are now available. However, limited data have been reported as regards their effects on patients with renal impairment.⁷⁶

In patients with stages 4 to 5 chronic kidney disease who are eligible for renal allograft, chemotherapy, including HDM/ASCT, should be considered either before or after transplantation. In patients who are not candidates for renal transplantation, administration of chemotherapy does not result in particular benefits.⁷⁶

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