

Clinical Analysis of 43 Patients with Light Chain Multiple Myeloma

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OBJECTIVE To investigate the clinical characteristics and laboratory findings of patients with light-chain multiple myeloma.

METHODS Forty-three patients with light chain myeloma over a 13-year period were analyzed retrospectively and 43 cases with IgG type myeloma in the same period were used as control.

RESULTS Of the 43 patients, 28 were male, 15 were female, with an overall mean age of 57 years (range, 36–71). At the time of onset, the main symptoms were fatigue and dizziness (23 cases, 53.5%) and bone pain (25, 58.1%). The main signs were anemia (28, 65.1%) and bone pressure pain (23, 53.5%). Of 39 patients with determined staging, 38 were in stage III and 1 stage I. Renal function examinations were performed for 31 patients. Among them, 16 were in stage III_b and 15 in III_a. Hypercalcemia (≥ 3 mmol/L) occurred in 2 cases. Of 18 patients, 3 had proteinuria ≥ 12 g per 24 hours. Osteolytic lesions appeared in 27 of 31 cases. No abnormal globulin peaks were found in the serum protein electrophoretic bands. Serum and urine immunoelectrophoresis showed that 10 cases were kappa light chain, 29 were lambda light chain and 4 were both. Nineteen patients received chemotherapy, of which 8 cases obtained complete remission and 11 had no remission.

CONCLUSION Because of poor differentiation, skeletal destruction and renal dysfunction, light chain multiple myeloma patients have meager therapeutical efficacy and poor prognosis.

KEYWORDS: multiple myeloma/light chain, serum/urine immunoelectrophoresis, quantity of light chain in urine.

Multiple myeloma is the most common type of plasma cell neoplasm. It can be classified into IgG, IgA, IgD and light chain types immunologically, in which 15–20 percent are found to be a light chain type. The neoplastic cells of this type synthesize and excrete only monoclonal light chain. Because of poor differentiation of tumor cells, widespread skeletal destruction and severe renal dysfunction, the prognosis of patients with light-chain myeloma is poor. In order to further understand this disease, we retrospectively analyzed 43 patients with light chain myeloma admitted to our hospital over a 13-year period.

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MATERIALS AND METHODS

Patient selection

From January 1990 to February 2003, a series of 224 multiple myeloma patients were admitted to our clinic and were classified immunologically. Among them, 43 were light-chain type. Forty-three cases of the IgG type myeloma in the same period were used as controls. All the diagnosed patients conformed to the diagnostic criteria of multiple myeloma,^[1] the clinical staging being based on the Durie and Salmon system,^[2] and the criteria of therapeutical response based on reference to Zhang.^[1]

Laboratory examination

Prior to therapy, the hemogram, bone marrow classification, immunoglobulin level, serum and urine immunoelectrophoresis were surveyed for all patients. The most of them had undergone bone marrow pathologic examinations, hepatic and renal function tests, serum protein electrophoresis analysis, bone radiography and determination of the quantity of 24-hour urinary protein and serum calcium level. A quantitative urine light-chain assay was also performed for some patients. The clinical manifestations, laboratory characteristics and therapeutical conditions were analyzed.

Statistical analysis

All statistical analysis was performed using the *U* test.

RESULTS

General features

There were 28 male and 15 female patients with a

mean age of 57 years (range, 36~71). Ten patients were 65 years or older and 12 patients 50 years or younger. The interval from onset to diagnosis was 1 month to 3 years with a mean time of 8.0 months.

Symptoms and signs

At the time of onset, the main symptoms were as follows: fatigue and dizziness 23(53.5%); bone pain 25 (58.1%); fever 5 (11.6%); an extramedullary mass 2 (4.7%); positive proteinuria 1 (2.3%) and jaundice 1 (2.3%). The main signs were pallor 28 (65.1%), bone pressure pain 23 (53.5%), hepatomegaly 2 (4.7%) and splenomegaly 1 (2.3%).

Clinical staging

Of 39 patients whose clinical staging was established at the time of admission, 1 was in stage I, and 38 in stage III. Renal function tests were performed on 31 patients, 15 in stage III_A and 16 in III_B (Table 1).

Laboratory findings

Blood routine examination

Of 43 patients, 13 had hemoglobin ≥ 100 g/L, 7 between 85 g/L and 100 g/L, and 23 <85 g/L, with the lowest being 50 g/L. Twelve had a platelet count $<100 \times 10^9/L$, the lowest count was $17 \times 10^9/L$. Myeloma cells were examined in the peripheral blood in 3 cases, the highest content being 12%.

Examination of bone marrow smear

Twelve-one cases showed active proliferative bone marrow, 11 were hypercellular, 1 were intensely hypercellular and 7 were hypocellular. The counts of myeloma cells ranged from 0 to 97% (12 cases <15 %, 2 cases 0 in iliac bone marrow).

Table 1. The differences between light chain type and IgG type multiple myeloma

Types	n	Age (years)	Staging*			Hemoglobin (g/L)	Platelets ($\times 10^9/L$)	Calcium# ($\geq 3mmol/L$)	Albumin* ($>35g/L$)	Plasma cells in bone marrow%	Quantity of Urine Protein($\geq 12g/24h$)	Renal dysfunction*	Osteolytic*
			I	II	III								
Light chain	43	57	1/39	0	38/39	76	133	2/23	25/28	38	3/18	16/31	27/31
IgG-type	43	61	0	5/40	35/40	75	158	2/26	5/32	35	0	10/34	20/34

*Indicates $P < 0.01$ between the two types, # Indicates $P > 0.05$ between the two types.

Bone marrow biopsy

Bone marrow pathological examinations were performed in 20 patients with the finding that marrow proliferation ranged from hypocellular to intensely hypercellular. Eighteen cases were classified based on pathological findings: 8 plasma cell type, 3 small cell type, 2 plasma blastic cell type, 2 polymorphic cell type, 1 had myelofibrosis and 3 a normal myelogram.

Serum protein electrophoresis

Serum protein electrophoresis was conducted for 30 patients: 4 had monoclonal (M) protein with the contents of 3.4%, 5.2%, 8.0% and 24%, respectively, occurring in the gammaglobulin region. The remaining 26 patients had normal serum protein electrophoresis without M protein.

Serum and urine immunoelectrophoresis

The serum and urine were examined by immunoelectrophoresis in all cases, 10 of whom were kappa light chain, 29 were lambda light chain and 4 were the both. The serum immunoglobulins IgG, IgA and IgM were normal, lower or absent.

Quantity of the urine light chain

Quantitative analysis for urine light chain was performed in 6 patients. The contents of urine kappa light chain in 2 patients with kappa type were 18.9 g/L and 4.29 g/L, respectively. The contents of urine lambda light chain in 4 patients with lambda type were 3.61 g/L, 14.9 g/L, 11.3 g/L and 0.775 g/L, respectively.

Quantity of serum immunoglobulin

The quantity of immunoglobulin was determined in 38 cases with the results of IgG ranging from 2.99 g/L to 13.2 g/L (average 6.86 g/L), IgA from 0.07 g/L to 3.16 g/L (average 0.66 g/L) and IgM from 0 to 4.50 g/L (average 0.65 g/L).

Serum albumin determination

Of 28 patients examined, 25 had levels of > 35 g/L and $3 \leq 35$ g/L.

Serum calcium levels

Of 23 patients examined, 2 were shown to have hypercalcemia (≥ 3 mmol/L), with concomitant renal insufficiency.

Quantity of 24-hour's proteinuria

Of 18 examined, 10 had proteinuria < 4 g per 24 hours, 5 ranged from 4 g to 12 g per 24 hours, 3 ≥ 12 g per 24 hours. Of 4 patients with the proteinuria ≥ 10 g per 24 hours, 3 case (75%) presented with renal dysfunction. Of 9 patients with the proteinuria < 10 g per 24 hours, 3 cases (33%) had renal dysfunction.

Renal function

Prior to therapy, renal function was evaluated in 31 cases. Renal dysfunction occurred in 16 cases, 6 of whom were at the uremic stage (4 cases were lambda type, 2 cases kappa type).

Skeletal radiography

Of 31 patients examined, 27 manifested osteolytic lesions, 1 osteoporosis and 3 were normal in appearance.

The difference between light chain type and IgG type multiple myeloma

In comparison with the clinical stage, serum albumin, quantity of proteinuria, renal dysfunction and osteolytic lesions between the two types, the differences were significant ($P < 0.01$), while the difference in the serum calcium level was not significant ($P > 0.05$) (Table 1).

Response to the therapy

Nineteen patients were treated by routine chemotherapy for more than 3 cycles, the regimens of which were M2 or MP, or combined with interferon- α , thalidomide; 2 cases received plasmapheresis and hemodialysis; 1 case was administered alternative hemi-irradiation; and 1 case accepted allogeneic peripheral blood stem cell transplantation. Among them, 8 cases obtained complete remission (3 cases received chemotherapy for more than 6 cycles), 11 cases had no remission (6 cases received more than 10

cycles).

DISCUSSION

Because the capability of bone marrow plasma cells to secrete the heavy chain is blocked, i.e. selectively suppressed, the synthetic ratio of heavy chain to light chain unbalanced, with light-chain myeloma often producing more light chain than heavy chain. Secreted into the peripheral blood, the light chain with low molecular weight (20,000~23,500) is excreted through kidney, presenting with concomitant light-chain-type M proteinemia and/or Bence Jones proteinuria. Bence Jones proteins, which are filtered through the glomeruli, have a direct toxicity on renal collecting tubules and induce renal damage.^[3]

Recent studies have showed that using fluorescence in situ hybridization, the translocations t (11;14) was associated with light-chain multiple myeloma, even though the progression and overall survival were similar for patients with or without t (11;14).^[4] There was a report that most light chain multiple myeloma cases presented with one IgH allele with a germline configuration (including the DJ region), the second allele being usually involved in an aberrant recombination. Of note, most of these translocations occurred close to (or at) switch regions. Light-chain multiple myeloma is due to the absence of a normal IgH rearrangement at the DNA level, reflecting possible abnormalities in the IgH gene recombinations during B-cell maturation.^[5]

It was reported that light-chain multiple myeloma accounted for 15~20% of all multiple myelomas.^[5,6] At our hospital, the incidence rate of light chain myeloma was 19.2 % (43/224 cases), similar to the previous reports. Besides the clinical and morphological characteristics, the diagnostic criteria of light chain myeloma were as followed: ① Bence Jones protein in the urine is positive. ② Serum protein electrophoresis occasionally reveals monoclonal light chain, without other M proteins. ③ All Ig levels in the serum are lower. ④ There are osteolytic lesions in bones. All 43 patients from our hospital conformed to the above criteria.

The initial symptoms and signs often present with

bone pain, paleness (anemia) and fatigue, possibly in combination with fever, jaundice, extramedullary mass, proteinuria, hepatomegaly and splenomegaly. Recently there were two cases presenting with polyarthritis, mimicking rheumatoid arthritis,^[7] and a case associated with extra-skeletal spread to lymph nodes, spleen and liver.^[8] In contrast to the IgG type, the patients with light-chain type are younger, mostly being in clinical stage III at initial diagnosis ($P<0.01$), with significant renal dysfunction ($P<0.01$). In addition, there are more patients with 24-hour proteinuria ≥ 12 g/L ($P<0.01$), bone X-rays indicating multiple osteolytic lesions ($P<0.01$) and the level of serum albumin is higher ($P<0.01$).

Patients with light-chain myeloma, displayed a high excretion of Bence Jones protein in the urine (>10 g/24 hours) and had renal insufficiency more often than patients with lower protein excretion, which was in accordance with other reports.^[3] In addition, renal insufficiency was related to advanced disease and the serum creatinine level at presentation was significantly associated with survival.^[9] Sixteen patients with light-chain myeloma from our hospital who were in III stage had renal dysfunction.

Diagnosis of multiple myeloma can not be eliminated without an abnormal globulin peak in the serum protein electrophoresis bands, because light-chain myeloma often presents without M protein.^[10] Therefore, in the diagnosis and differential diagnosis of light-chain myeloma, serum and urine immunoelectrophoresis must become part of a routine examination. To determine multiple myeloma types, serum and urine immunoelectrophoresis was conducted in all 43 patients. For 6 of these patients a quantitative determination of their urine light chain was performed, with the results similar to the qualitative determination. During the therapeutic progress, monitoring the light chain in urine quantitatively and qualitatively was of benefit to evaluate the therapeutic effect and disease process. However, there was a report using protein electrophoresis that after 2 years undergoing a stem cell transplant, a patient with a lambda light-chain multiple myeloma presented with a large serum M-spike (23 g/L). The spike consisted of monoclonal lambda light

chain as hexameric aggregates without a heavy chain.^[11]

In our studies, at initial diagnosis, 2 patients with light-chain myeloma presented with hypoplastic and an absence of plasma cells in the iliac bone marrow. At the same time, a sternum marrow aspirate was performed. One patient was hyperplastic with 13.0 % plasma cells and I had active proliferative bone marrow with 3.5 % plasma cells. In combination with the results of serum and urine immunoelectrophoresis, both were diagnosed as lambda-light-chain multiple myeloma. Therefore, at the diagnosis of light-chain myeloma, it is important to know if there is light chain in the serum or urine, while plasma cells in bone marrow are less important. Bone marrow aspirates through multiple areas play an important role.

Because of the poor therapeutical effect, patients with light chain myeloma had a significantly shorter overall survival (OS) and event-free survival (EFS) and need repeated and continuous chemotherapy.^[12] and few patients may obtain partial remission or improvement. An early response to MP indicates an obvious survival advantage.^[13] The patients with renal insufficiency must be treated with plasmapheresis and hemodialysis therapy in a timely manner in order to prolong survival. In recent years, with the progress of chemotherapy and hematopoietic stem cell transplantation, it has become possible to increase the remission rate of patients with light-chain myeloma. Trullemans et al.^[14] reported a case of a 54-year-old female patient with stage III_A kappa light chain myeloma who relapsed 7 years after syngeneic bone marrow transplantation. The relapse occurred as a massive soft tissue plasmacytoma in the leg, developing after local trauma. Savage et al.^[15] also reported a case of a 44-year-old woman with kappa light-chain myeloma undergoing allogeneic stem cell transplantation who developed paraspinal plasmablastic myeloma in the absence of paraprotein in urine or myeloma in the marrow after twenty months. At 30 months, she developed myelomatous meningitis. The leptomeningeal disease led to death at 38 months. Our hospital reported 1 patient with stage III_A lambda light-chain myeloma who did not obtain remission after repeated chemotherapies but then

accepted allogeneic peripheral blood stem cell transplantation and obtained complete remission. Sirohi et al.^[16] compared the prognoses of patients with light chain, IgG and IgA types. They performed autologous hematopoietic stem cell transplantation and found that the median OS and EFS of patients with light-chain type was significantly shorter than that of patients with IgG myeloma. However, among those patients who achieved complete remission there was no difference in OS and EFS between IgG and light chain myeloma. Thalidomide can effectively control the rate of myeloma relapse after high-dose chemotherapy, and may be especially useful in resistant cases or those unable to tolerate further chemotherapy. A patient with kappa light chain multiple myeloma relapsed 6 months after receiving 180 mg/m² of melphalan and an autograft. Thalidomide was administered, and the patient achieved near-complete remission within 6 months and was in near-complete remission nine months after starting thalidomide.^[17]

REFERENCES

- 1 Zhang ZN, Shen T. The diagnostic and therapeutical criteria of hematology. The second edition. Beijing: Scientific publishing house. 1998; 373-379.
- 2 Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. *Cancer*. 1975; 36:842-854.
- 3 Knudsen LM, Hippe E, Hjorth M, et al. Renal function in newly diagnosed multiple myeloma—a demographic study of 1353 patients. The Nordic Myeloma Study Group. *Eur J Haematol*. 1994;53:207-212.
- 4 Chang H, Sloan S, Li D, et al. The t (4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. *Br J Haematol*. 2004;125: 64-68.
- 5 Magrangeas F, Cormier ML, Descamps G, et al. Light-chain only multiple myeloma is due to the absence of functional (productive) rearrangement of the IgH gene at the DNA level. *Blood*. 2004;103:3869-3875.
- 6 Kyle RA, Gertz MOA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003; 78:21-33.
- 7 Hamza S, Landolsi F, Sahli H, et al. Light chain multiple myeloma revealed by an amyloid arthropathy (A report of two cases). *Rev Med Interne*. 2004;25:390-394.
- 8 Haidar JH, Bazarbachi A, Nasr MR, et al. Signet ring-like

- light chain myeloma with systemic spread. *Eur J Haematol.* 2003;70:249–250.
- 9 Chow CC, Mo KL, Chan CK, et al. Renal impairment in patients with multiple myeloma. *Hong Kong Med J.* 2003; 9:78–82.
- 10 van Zaanen HC, Diderich PP, Pegels JG, et al. Renal insufficiency due to light chain multiple myeloma. *Ned Tijdscha Geneeskd.* 2000;144:2133–2137.
- 11 Abraham RS, Charlesworth MC, Owen BA, et al. Trimolecular complexes of lambda light chain dimmers in serum of a patient with multiple myeloma. *Clin Chem.* 2002;48:1805–1811.
- 12 Sirohi B, Powles R, Mehta J, et al. The implication of compromised renal function at presentation in myeloma: similar outcome in patients who receive high-dose therapy: a single-center study of 251 previously untreated patients. *Med Oncol.* 2001;18:39–50.
- 13 Schaar CG, Kluin-Nelemans JC, le Cessie S, et al. Early response to therapy and survival in multiple myeloma. *Br J Haematol.* 2004;125:162–166.
- 14 Trullemans F, Schots R, Storma G, et al. Late and localized extramedullary relapse of a light chain kappa myeloma after syngeneic bone marrow transplantation. *Bone Marrow Transplant.* 2000;25:115–117.
- 15 Savage DG, Mears JG, Balmaceda C, et al. Leptomeningeal relapse of multiple myeloma following allogeneic stem cell transplantation. *Key Res.* 2001;26:689–692.
- 16 Sirohi B, Powles R, Kulkarni S, et al. Comparison of new patients with Bence-Jones, IgG and IgA myeloma receiving sequential therapy: the need to regard these immunologic subtypes as separate disease entities with specific prognostic criteria. *Bone Marrow Transplant.* 2001;28:29–37.
- 17 Zomas A, Anagnostopoulos N, Dimopoulos MA. Successful treatment of multiple myeloma relapsing after high-dose therapy and autologous transplantation with thalidomide as a single agent. *Bone Marrow Transplant.* 2000;25:1319–1320.