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Case report

Clinical characteristics and prognostic significance of immunoglobulin isotype switch in patients with multiple myeloma

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HIGHLIGHTS

- Among 376/506 (74.3%) patients with multiple myeloma (MM) who relapsed, 13 (3.5%) exhibited Ig isotype switching
- Eleven remained sensitive to therapy, exhibiting at least a partial response
- The different clinical manifestations and Ig phenotypes of MM recurrence from those at initial diagnosis provides direct clinical evidence for MM clonal evolution

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ABSTRACT

Immunoglobulin (Ig) isotype switching in multiple myeloma (MM) is a rare form of clonal evolution. The aim of this study was to investigate the clinical features and prognostic significance of Ig isotype switching by observing Ig transformation in patients with relapse. A retrospective analysis was performed on 506 patients with newly diagnosed MM who were treated at our hospital from February 2005 to February 2020. The patients who experienced relapse were divided into the following four groups according to Ig phenotype: original paraprotein, complete isotype switching, light chain escape (LCE),and non-secretory clinical relapse. For comparative purposes with the original paraprotein group, the last three groups were pooled as the transformation group. Among the 506 included patients, 376 (74.3%) relapsed. Among them, 13/376 (3.5%) patients exhibited Ig isotype switching, including 3 with complete isotype switching, 3 with LCE, and 7 with non-secretory clinical relapse. Eleven remained sensitive to therapy, exhibiting at least a partial response. Seven patients survived for at least 20 months after relapse. The median overall survival time of the LCE, clinical relapse, and complete isotype switching groups were 6, 20, and 76 months, respectively, after recurrence. The clinical manifestations and Ig phenotypes of MM recurrence were different from those at the initial diagnosis in the 13 patients exhibiting Ig isotype switching. These differences vividly conveyed the heterogeneity of the clonal populations and provides direct clinical evidence for MM clonal evolution.

Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by clonal proliferation of malignant plasma cells. It is currently incurable and consists of multiple subclones and high tumor heterogeneity. Its heterogeneity has existed since monoclonal gammopathy of undetermined significance. Keats et al.[1] discovered the following three evolutionary paths in MM molecular biology: (1) the genomic stability path, that is, the genomes of clones at diagnosis and recurrence do not change; (2) the linear evolution path, in which the primary clone at the initial diagnosis evolves owing to acquired gene damage; and (3) the path of heterogeneous clonal mixtures with shifting predominant clones.[2,3]

In which the plasma cell genome obtains random gene mutations, and the dominant genome is selected depending on the bone marrow microenvironment. Even in patients with deep remission of the disease, MM exhibits long-term stability and undergoes clonal evolution, indicating that clonal evolution accompanies all stages of this disease.

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Brioli et al.[4] reported the largest clinical study on light chain escape (LCE) at the time of recurrence, emphasizing the importance of serum free light chain detection. In addition, they noted that the immunoglobulin (Ig) type can be used as a marker of clonal heterogeneity.[5]Hence, clonal evolution can be explained intuitively from a clinical point of view, but no similar studies have been published since theirs.

Inspired by the research of Brioli et al.,[4] we retrospectively analyzed all patients with primary MM who were treated in our center over the past 15 years, for changes in Ig at follow-up and their immunophenotypic changes after recurrence. The aim was to investigate the clinical features and prognostic significance of Ig isotype switching. We discovered cases of Ig isotype switching at the time of recurrence, including cases of complete transformation of Ig, which was not observed by Brioli et al.[4] As this study of patients with recurring MM and Ig transformation had such a long follow-up period, we believe that it provides direct clinical evidence for MM clonal evolution.

Case presentation

A retrospective analysis was performed on 506 patients with newly diagnosed MM who were treated in our hospital from February 2005 to February 2020. We adopted the diagnostic and efficacy criteria based on the diagnosis of the International Myeloma Working Group.[6]All 506 patients were followed up once every 2 months. Immunofixation electrophoresis (IFE) for hematuria was performed along with Ig quantitative examination when the patient relapsed. The patients who experienced relapse were divided into the following four groups according to Ig transformation. (1) Prototype: change in paraprotein level between maximum response and relapse ≥5 g/L and a ≥25% increase or a change of ≥200 mg/24 h in urine light chain. (2) LCE: heavy chain disappeared, light chain ≥5 g/dL or increased by ≥ 25%. (3) Clinical relapse: change in paraprotein between maximum response and relapse <5 g/L. (4) Complete isotype switch: New paraprotein ≥5 g/dL and new urine light chain ≥200 mg/24 h or from non-secretion to secretion. The median follow-up time was 98 (range, 14–203) months, and the follow-up period was up to February 2022.

For comparative purposes, groups 2–4 were pooled as the transformation group.

Up to February 2022, 376 patients (74.3%) relapsed. Among patients who relapsed, the type of Ig was consistent with that in the first diagnosis in 363 (96.5%), while 0.8% (3 of 376) relapsed with LCE (with a substantial increase in their light chain levels only), 1.9% (7 of 376) clinically relapsed with negative IFE results and normal free light chain, and 0.8% (3 of 376) relapsed with a complete isotype switch.

Comparisons of the clinical baseline data between the prototype and transformation groups revealed no significant differences in age, sex, myeloma type, Durie-Salmon stage, International Staging System (ISS) stage, simultaneous renal insufficiency, chromosomal abnormalities, or fluorescence in-situ hybridization results. However, the recurrence of extramedullary tumors was significantly higher ($\chi^2 = 48.603$, $P < 0.001$) in the transformation groups (8/13, 61.5%) than in the prototype group (30/363, 8.3%). The comparisons between the prototype and transformation groups are presented in Table 1.

Thirteen patients exhibited at least a partial response (PR) after induction treatment, among whom 8 exhibited a complete response (CR), 4 a very good PR (VGPR), and 1 a PR. The median overall survival (OS) was 72 months (range, 14–203) months. Eleven patients exhibited a response after isotype switching, 5 of whom exhibited a CR, 2 a VGPR, and 4 a PR. The median survival time of patients with LCE was only 6 (range, 3–20) months, that of patients with clinical recurrence was 20 (range, 4–62) months, and that of patients with a complete transformation was 76 (range, 8–99) months after isotype switch. The characteristics of the 13 patients who exhibited isotype switching are presented in Table 2, and case 10 was selected for a detailed description in this report [Supplementary Figure 1].

Table 1
Comparison of the data between the prototype and transformation groups.

Characteristics	Recurrence of prototype ($n = 363$)	Recurrence of transformation ($n = 13$)	χ^2	P
Median age (years)	59	57	–	–
Age ≥65 years, *n* (%)	111 (30.6)	2 (15.4)	0.378	0.240
Sex, male, *n* (%)	207 (57.0)	6 (46.2)	0.604	0.437
Myeloma type, *n* (%)				
IgG	176 (48.5)	4 (30.8)	1.452	0.437
IgA	76 (20.9)	4 (30.8)	0.724	0.395
Light chain	84 (23.1)	2 (15.4)	0.428	0.513
DS stage, *n* (%)				
I	9 (2.5)	0	–	–
II	15 (4.1)	1 (7.7)	0.502	0.479
III	339 (93.4)	12 (92.3)	0	>0.990
ISS stage, *n* (%)				
I	116 (32.0)	4 (30.8)	0.008	0.928
II	99 (27.3)	2 (15.4)	0.903	0.342
III	148 (40.8)	7 (53.8)	2.300	0.129
Renal insufficiency, *n* (%)	37 (10.2)	2 (15.4)	0.364	0.546
Chromosomal, *n* (%) abnormalities	14 (3.9)	1 (7.7)	0	>0.990
FISH, *n* (%)				
1q21	66 (18.2)	1 (7.7)	0.363	0.547
17p13	26 (7.2)	2 (15.4)	1.231	0.267
Recurrence with extramedullary tumor mass, *n* (%)	30 (8.3)	8 (61.5)	48.603	<0.001

Prototype: Change in paraprotein level between maximum response and relapse ≥5 g/L and an increase ≥25% or a change of ≥200 mg/24 h in urine light chain. Recurrence of transformation included light chain escape, clinical relapse, and complete isotype switch. Light chain escape: heavy chain disappeared, light chain ≥5 g/dL or increased by ≥ 25%. Clinical relapse: change in paraprotein between maximum response and relapse of <5 g/L. Complete isotype switch: new paraprotein ≥5 g/dL and new urine light chain ≥200 mg/24 h or from non-secretion to secretion. Ig: Immunoglobulin; DS: Durie-Salmon; ISS: International staging system; FISH: Fluorescence in-situ hybridization.

Discussion

Brioli et al.[4] described four types of Ig changes in 520 patients with MM who relapsed: 10.4% with free LCE (only the free light chain increased); 49.6% with an paraprotein levels increase only; 35.2% with an increase in both free chain and paraprotein; and 4.8% with clinical relapse (but none of the chains increased). The median survival time of patients with free LCE was the shortest. However, as we detected increases only in free light chains over the past five years, we could not use the same classification method. Hence, we divided our cases into four types according to the Ig type.

The most commonly reported type of complete isotype switching is the emergence of a new oligoclonal Ig,[7] that is, a small amount of new M protein (<10 g/L or <200 mg/24 h),[8] especially in patients with a CR after autologous stem cell transplantation (ASCT). Among 177 MM patients who underwent ASCT from 2007 to 2016 and were assessed by Ye et al.,[7] 39 (22%) patients exhibited Ig switching, which was related to improvements in progression-free survival (PFS) and OS. Another study confirmed that patients who exhibited a CR after transplantation, more likely to have oligoclonal bands, had a better PFS and OS than those who did not exhibit oligoclonal bandsy.[9] The authors of that study stated that oligoclonal bands may be a manifestation of immune reconstruction after high-dose chemotherapy with ASCT. A similar phenomenon was discovered in the latest clinical trial of B-cell maturation antigen-targeted

Table 2
Characteristics of 13 patients with immunoglobulin isotype switch.

Characteristics	Age (years)	Sex	MM type	ISS stage	FISH before IS	OS1 (months)	Maximum response	Symptoms of IS	Type of isotype switch to	FISH after IS	Therapeutic regimen after IS	Maximum response after IS	OS2 (months)	Follow-up time (months)
Case 1	55	F	IgM-κ	I	N/A	71	CR	Bone lesion impairment	λ	11q13/14q32; 13q14 deletion	DVD/PCD	CR	76	147
Case 2	59	M	κ	III	Normal	28	CR	Multiple extramedullary tumors	No secretion	Normal	DECP/RDPACE	PR	42	70
Case 3	45	F	IgG-κ	III	Normal	59	CR	Intracranial extramedullary tumor	No secretion	Normal	BDPACE	VGPR	62	121
Case 4	66	M	IgD-λ	III	N/A	104	CR	Lymphadenopathy	IgG- κ	P53 deletion	R–CHOP/T	VGPR	99	203
Case 5	55	F	IgG-κ	III	N/A	82	CR	Bone lesion impairment	No secretion	Normal	MPT	CR	47	129
Case 6	62	F	IgA-κ	III	1q21	37	VGPR	Anemia	κ	Normal	T-DECP	PR	6	43
Case 7	63	F	IgG-κ	II	N/A	88	VGPR	Extramedullary tumor of right upper arm	κ	N/A	T-DECP	PR	20	108
Case 8	65	M	IgG-κ	II	N/A	69	VGPR	Anemia, thrombocytopenia	κ	N/A	BD	PD	3	72
Case 9	57	M	IgA-λ	III	P53	10	PR	Extramedullary tumor of lumbar	No secretion	P53 deletion	PAD/BDPACE/RID radiotherapy	PD	4	14
Case 10	56	F	κ	I	Normal	55	CR	Extramedullary maxillary tumor	No secretion	Normal	VAD/DECP/PAD/RCD	CR	14	77
Case 11	52	F	IgA-λ	III	Normal	14	CR	Extramedullary pelvic and mandibular tumors	No secretion	Normal	TAD/B-DECP/ radiotherapy	CR	20	34
Case 12	51	M	No secretion	I	Normal	9	VGPR	Extramedullary tumor, paraplegia	λ	Normal	B-DECP	PR	8	17
Case 13	50	M	IgA-λ	I	Normal	35	CR	Extramedullary tumor on the shin	No secretion	Normal	B-DECP	CR	5	40

Cases 1, 4, and 12 were exhibited complete transformation. Cases 6, 7, and 8 exhibited light chain escape. Cases 2, 3, 5, 9, 10, 11, and 13 exhibited clinical recurrence. IS: Isotype switch; MM: Multiple myeloma; F: Female, M: Male; N/A: Not applicable; ISS: International staging system; FISH: Fluorescence in-situ hybridization; Ig: Immunoglobulin; PR: Partial response; VGPR: Very good Partial response; CR: Complete remission; OS1: Survival time before isotype switch; OS2: Survival time after isotype switch; DVD: Daratumumab, bortezomib, and dexamethasone; PAD: Bortezomib, doxorubicin, and dexamethasone; PCD: Bortezomib, cyclophosphamide, and dexamethasone; RCD: Lenalidomide, cyclophosphamide, and dexamethasone; VAD: Vincristine, doxorubicin, and dexamethasone. BD: Bortezomib and dexamethasone; MPT: Melphalan, thalidomide, and dexamethasone. DECP: Cisplatin, etoposide, cyclophosphamide, and dexamethasone; RDPACE: Lenalidomide, cisplatin, doxorubicin liposomes, etoposide, cyclophosphamide, and dexamethasone; BDPACE: Bortezomib, cisplatin, doxorubicin liposomes, etoposide, cyclophosphamide, and dexamethasone; R–CHOP: Rituximab, doxorubicin liposomes, cyclophosphamide, and dexamethasone; T-DECP: Thalidomide, cisplatin, etoposide, cyclophosphamide, and dexamethasone; RID: Lenalidomide, ifosfamide, and dexamethasone.

chimeric antigen receptor-T-cell therapy: abnormal protein bands (APBs) were detected via serum IFE, distinct from the paraprotein present at diagnosis. The appearance of APBs may be associated with immune reconstitution and recovery of B-cell function.[10] The three cases of complete isotype switching in our study differed completely from that situation. First, the M protein concentration after transformation was very high in these cases. Second, a complete isotype switch was observed at the time of disease recurrence. Among them, two patients exhibited long-term CR after induction therapy (Ig transformation occurred 6 and 9 years, respectively, after the initial diagnosis) and the other patient exhibited new Ig types upon recurrence in the 6th month after transplantation. This type of recurrent clone may have originated from a low-level clone that could not be detected at the initial diagnosis, or it may have been branching, nonlinear recurrence, that is, random genetic variation and natural selection under limited resources.

LCE is the most commonly reported pathway of Ig switching. Our data revealed a low proportion of LCE, possibly because of the study limitations: the data were obtained from a single center and the study was retrospective.

In our study, seven patients exhibited clinical recurrence, with normal concentrations of Ig heavy and light chains in the blood and urine. Among them, six patients had extramedullary recurrence. Their pathologies suggested that they had plasmacytomas with nonlinear recurrence. Anagnostopoulos et al.[11] assessed 94 patients with advanced MM and 9 patients with newly diagnosed MM. They discovered an imbalance in the decrease in Ig and plasma cell infiltration of bone marrow in four patients whose bone marrow was heavily infiltrated by plasma cells, despite a decrease in the paraprotein levels ranging from 38% to 68%. Moreover, six patients relapsed within 5–9 months of exhibiting a PR, all exhibiting an increase in plasma cells in the bone marrow but not an increase in Ig in the serum or urine, including two patients exhibiting extramedullary recurrence. Similarly, the disease was highly invasive in our study; therefore, we infer that the responsible clones are primitive and unable to secrete Ig.

Our study demonstrated that the transformation of M protein can occur a long time after treatment of the disease, with a median of 55 (range, 9–104) months in our study, similar to the 42 (range, 12–189) months to occurrence of LCE reported by Kühnemund et al.,[12] reflecting the possibility of clonal evolution and a high heterogeneity of the disease. In previous studies, the sensitivity of therapy decreased after Ig transformation, the follow-up treatment was often ineffective, the prognosis was poor, and the median survival time of patients was 11 months. In particular, the median survival time was shorter than the 10 months for patients with extramedullary infiltration.[13] However, in our study, follow-up treatment was effective in 11 of the 13 patients with immunoglobulin isotype switching. Seven patients survived for at least 20 months after relapse. The curative effect on patients exhibiting LCE was the poorest among those with immunoglobulin isotype switching; their median survival time was only 6 months after isotype switching. Patients with clinical recurrence survived a median time of 20 months, and the curative effect on patients exhibiting complete transformation was satisfactory, yielding a median survival time of 76 months. This also indicates that the degree of malignancy of MM derived via branching clonal evolution may not be higher than that derived via linear evolution.

In addition, An et al.[14], reported at least one cytogenetic abnormality per patient at the time of diagnosis in their observational study of 193 patients with MM. A majority of the patients (63%) had persistent cytogenetic abnormalities in their residual plasma cells, which laid a foundation for clonal evolution at the time of recurrence and new mutations when relapse occurred. In our study, gene sequencing was conducted for the two patients exhibiting complete transformation; one had a mutation in the *CREBBP* gene, and the other had *SF381*, *ATM*, and *IL7R* mutations, which may explain molecular mechanism for the clonal evolution marked by Ig transformation in these patients.

The advantage of this research is that some very special Ig isotype switching cases had been observed through more than 10 years of continuous following-up.Such studies are rarely done. With the popularization of free light chain detection, the follow-up of free light chains in each stage would be helpful for monitoring MM clonal evolution, this is the direction of our research and exploration in the future. In summary, the clinical manifestations and Ig phenotypes of MM recurrence were different from those at the initial diagnosis in the 13 patients exhibiting Ig isotype switching. These differences vividly conveyed the heterogeneity of the clonal populations and provides direct clinical evidence for MM clonal evolution.

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Author contributions

Minqiu Lu designed the study and wrote the manuscript. Bin Chu, Yutong Wang, Lei Shi, Shan Gao, Lijuan Fang, Qiuqing Xiang, Xi Liu, Yuehua Ding, Yuan Chen, Xin Zhao, and Mengzhen Wang collected and analyzed the data. Bin Chu and Yutong Wang performed the visualization. Li Bao and Kai Sun supervised and administered the study.

Ethics statement

All participants signed an informed consent form, and the study was approved by the Ethics Committee of Beijing Jishuitan Hospital and the Fourth Medical College of Peking University (Beijing, China) (Approval code: JST201907-04).

Data availability statement

The data supporting the findings of this study are available upon request to the corresponding author.

Conflict of interest

None.

Acknowledgment

We would like to thank the faculty members who collected the samples and assembled the data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2022.11.002.

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