Heliyon 10 (2024) e28950

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Disease-controlled multiple myeloma in a patient with 17p gain and t(4;14): A case report

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ARTICLE INFO

Keywords:
Case report
Multiple myeloma
17p gain
t(4;14)
Prognosis

ABSTRACT

Cytogenetic karyotypes such as t(4; 14), del(17p), t(14; 16), t(14; 20), and *TP53* mutations are associated with high-risk multiple-myeloma (MM) and indicate poor prognosis. Therefore, cytogenetic testing is extremely important for determining prognosis of MM. However, the aberrant karyotypes reported in the current literature are incomplete. The cytogenetic karyotype 17p gain has not received widespread attention, and its relationship with MM prognosis is unknown; additionally, the prognosis of 17p gain associated with t(4; 14) has not been studied in depth. Therefore, we introduce a special case in which a patient had both 17p gain and t(4; 14). An 81-year-old woman was admitted to the Affiliated Hospital of Shandong University of Traditional Chinese Medicine for stomach discomfort. The patient had no relevant medical history. Laboratory tests, immunophenotyping, and haematological results suggested MM, and cytogenetic tests indicated 17p gain and t(4; 14) with no other abnormalities. She was treated with two different chemotherapeutic regimens and achieved very good partial response, but eventually experienced biochemical relapses after discontinuing therapy. However, she eventually achieved good disease control with a bortezomib, lenalidomide, and dexamethasone-based regimen; she has survived longer than 5 years, much longer than the 1 year reported for MM patients with t(4:14), and been progression-free more than 3 years. We use this case to explore the possible relationship between the 17p gain and prognosis of patients with MM, as well as the treatment of MM with high-risk cytogenetic karyotypes. This case enriches the clinical application of cytogenetic analysis and adds important indicators for the prognosis of MM patients.

1. Introduction

Multiple myeloma (MM), which accounts for approximately 10% of all haematologic malignancies [1], is characterised by

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https://doi.org/10.1016/j.heliyon.2024.e28950
Received 8 June 2023; Received in revised form 26 March 2024; Accepted 27 March 2024
Available online 2 April 2024
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hyperplasia of myeloplasmacytoma and complete monoclonal immunoglobulin (IgG, IgA, IgD, or IgE) or Bence Jones protein (free monoclonal kappa or γ light chain). The incidence of MM is approximately 5 per 100,000 people [2], with a slight male predominance [3]. The clinical signs and symptoms of MM include hypercalcaemia, renal damage, anaemia, and multiple osteolytic lesions.

In MM, t(4; 14) often indicates a high risk of disease and poor prognosis [4], as do del (17p), t(14; 16), t(14; 20), p53 mutations, and other abnormal cytogenetic karyotypes. Patients with two or more of these genetic abnormalities are considered to have high-risk MM, and they have tend to have poorer therapeutic response and shorter survival time patients with normal cytogenetics [4]. The clinical risk of patients with MM is stratified using the International Myeloma Stratification and Risk-Adapted Therapy (mSMART) guidelines, with cytogenetic characteristics being one of the most influential factors [5]. Clinical studies have found that under the same treatment regimen, patients with t(4; 14) do not achieve median progression-free survival (PFS), whereas those without t(4; 14) have a PFS of 19.450 months [6], which shows that t(4; 14) is closely related to the prognosis of MM, and patients with this cytogenetic karyotype are unlikely to have good disease control. IKEMA (NCT03275285) is a phase 3 clinical study that similarly confirmed that MM patients with the t(4; 14) cytogenetic karyotype generally have poorer outcomes [7]. Pre-specified interim efficacy analyses showed that patients with relapsed MM without t(4; 14) have significantly improved PFS compared to those with t(4; 14) ($p < 0.01$) and are more likely to be minimal residual disease-negative (29.6% vs 13.0%), have very good partial response (VGPR) (72.6% vs 56.1%), and have complete response (39.7% vs 27.6%) [7].

del(17p) is the most significant poor prognostic marker in MM and is observed at diagnosis in 5–10% of patients. *TP53* is located on chromosomal band 17p13 and is thought to be the gene responsible for del(17p) in MM. Biallelic inactivation of *TP53* is associated with worse prognosis in patients with del(17p) [8].Mutations in *TP53* are enriched in clones with del(17p) in MM, and deletions and mutations in *TP53* occur in approximately 9% and 5% of patients with NDMM, respectively [9]. Autologous haematopoietic stem cell transplantation in combination with bortezomib has been found to help overcome the adverse effects of del(17p) [10], but the occurrence of this abnormal cytogenetic event remains concerning. By contrast, 17p gain has not received widespread attention, and its relationship with MM prognosis is unknown. However, based on the effect of del(17p), it could be speculated that 17p gain is a predictor of good prognosis in MM. Determining the clinical impact of this karyotype and the survival time of patients with MM with del(17p) and 17p gain karyotypes would be helpful for predicting prognosis based on cytogenetic abnormalities.

The combination of t(4; 14) and 17p gain in a patient with MM has not been reported. Here, we describe our experience with a patient with MM 17p gain (*TP53* × 3) accompanied by t(4; 14) (*IGH/FGFR3*), including treatment response and survival, to understand the relationship between 17p gain and prognosis in MM.

2. Case report

An 81-year-old woman was admitted to the Affiliated Hospital of Shandong University of Traditional Chinese Medicine for physical examination in January 2018 due to stomach discomfort. She was Han nationality, married, a retiree, and born in Licheng District, Jinan City, Shandong Province. The patient's admission symptoms were as follows: mental and physical strength, no fever or cough, no dizziness or panic, normal sleep, and two bowel adjustments. The patient had no relevant medical history. She had not taken any medication in the past; had no allergies to vaccines, drugs, or food; and had no family or genetic history or history of infectious diseases, such as tuberculosis.

The biochemical results at admission showed the following: albumin, 25.2 g/L; globulin, 105.6 g/L; M protein, 64.6134 g/L; β2 microglobulin, 3.4 mg/L; lactate dehydrogenase, 65 U/L; κ light chain (blood), 0.806 g/L; λ light chain (blood), 43.10 g/L; λ light chain (urine), 0.105 g/L; IgG, 91.8 g/L; IgA, <0.25 g/L; IgM, 0.186 g/L; and haemoglobin, 81 g/L. Detailed laboratory findings are presented in Table 1.

In view of the anomalous laboratory test results, the patient was transferred to the haematology unit, and further tests were conducted. We observed active bone marrow hyperplasia, with myeloma cells accounting for 34.5%, and binuclear tumour cells were visible. We next performed immunophenotyping of the haematological cells. Abnormal cell populations were seen in the distribution of the CD45/SSC and CD45/CD38 subpopulations. We observed strong CD45/SSC and CD45/CD38 positivity, and SSC-positive cells were larger than nucleated red blood cells, accounting for about 27.1% of nucleated cells. These cells expressed CD28, CD38, CD56,

Table 1
Patient's laboratory test results.

Parameter	Value	Reference range
Albumin	25.2 g/L	35–55g/L
Globulin	105.6 g/L	15–35 g/L
M protein	64.6134 g/L	0.6–2.5 g/L
β2 microglobulin	3.4 mg/L	0–0.2 mg/L
Lactate dehydrogenase	65 U/L	200–380 U/L
κ light chain (blood)	0.806 g/L	6.29–13.50 g/L
λ Light Chain (Blood)	43.10 g/L	3.13–7.23 g/L
λ Light Chain (Urine)	0.105 g/L	0–0.05 g/L
IgG	91.8 g/L	7.51–15.60 g/L
IgA	<0.25 g/L	0.82–4.53 g/L
IgM	0.186 g/L	0.46–3.04 g/L
Haemoglobin	81 g/L	110–150 g/L

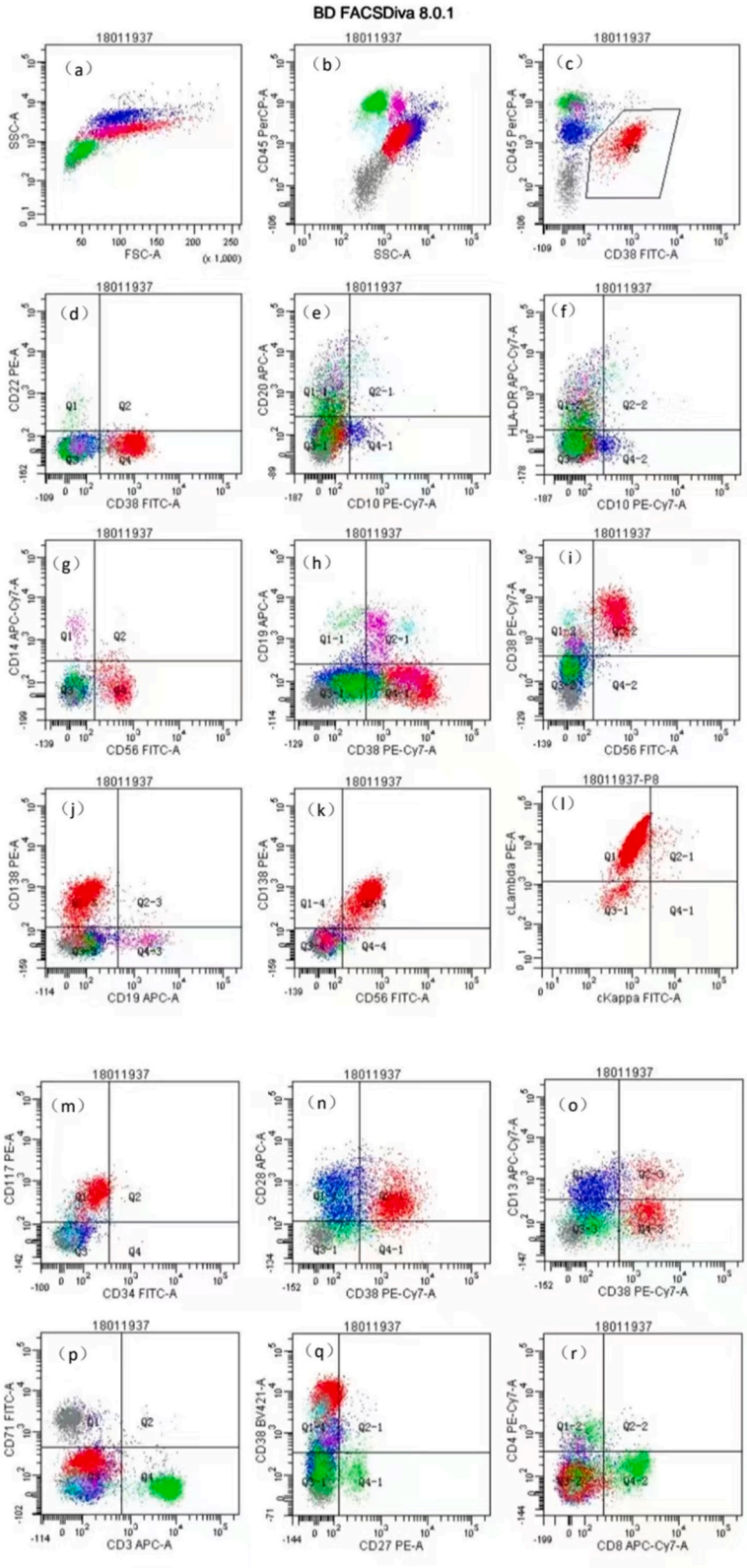

Fig. 1. Immunophenotyping of haematological subpopulations by flow cytometry at presentation.

CD117, CD138, and cLambda, but not CD19; therefore, we considered the diagnosis to be MM or plasma cell leukaemia (Fig. 1). Pathological analysis of the bone marrow biopsy suggested plasma cell myeloma, and there was IgG-LAM M proteinemia. FISH was positive for *TP53* locus amplification and *IGH/FGFR3* locus fusion (Fig. 2), and the karyotype showed 50 chromosomes (+3, +8, +17, +19 [3]/46, and XX) [11]. We next performed radiography of the sternum and skull. We observed multiple punctures that had caused bone destruction in the skull, consistent with the presentation of myeloma; low or suspected low density of the proximal bilateral humerus, bilateral scapular glenoids, right clavicle, and bilateral partial ribs; and degeneration of the right acetabulum. The sternal bone was not clearly visible.

(Cell Population Proportion: Lymphocyte(Green): 16.2%, Monocyte(Purple): 4.8%, Granulocyte(Blue): 32.8%, Abnormal cell (Red): 27.1%, Blast Cell(Sky Blue): 1.8%, Erythroblast(Gray): 17.3%. Antigens examined in this test: HLA-DR、CD3、CD4、CD8、CD10、CD13、CD14、CD19、CD20、CD22、CD27、CD28、CD34、CD38、CD56、CD71、CD117、CD138、cLambda、cKappa、CD45[Fig.1(a)-Fig.1(r)]. Instrument: Flow cytometer.)

The proportion of clonal bone marrow plasma cells in the patient was >10%, and the flow cytometry results showed CD38, CD138, and cLambda positivity and cKappa negativity, i.e. light chain restriction expression, accompanied by anaemia and bony lesions. Therefore, according to the diagnostic criteria of the International Myeloma Working Group for the diagnosis of MM and related diseases [12], we diagnosed the patient with multiple myeloma (IgG-LAM type) in our hospital in January 2018 (DS IIIA, ISS II, R–ISS II, and mSMART high-risk).

The patient began treatment with bortezomib (1.3 mg/m^2 d1/4/8/11) and dexamethasone (20 mg d1/2/8/9/15/16/22/23) on January 24, 2018. She achieved VGPR; however, she decided to discontinue treatment on December 22, 2018. On October 10, 2019, we identified biochemical relapse, and she was administered oral ixazomib (4 mg d1/8/15), lenalidomide (10 mg d1-21), and dexamethasone (20 mg d1/2/8/9/15/16/22/23). She achieved VGPR and decided to discontinue treatment on November 6, 2020. In June 2021, there was another biochemical recurrence. The bone marrow was re-examined, and the bone marrow smear showed that myeloma cells accounted for 7% of all cells, and the morphology was tumour-like. Therefore, we repeated immunophenotyping and found that lymphocytes accounted for approximately 23.3% of nucleated cells, of which CD19$^+$ cells accounted for approximately 1.7%. These cells expressed HLA-DR, CD19, CD20, CD22, sIgM, cIgM, FMC-7, cLambda, and Lambda, indicating abnormal monoclonal B lymphocytes. CD45dim/CD38st cells accounted for approximately 2.2% of nucleated cells and expressed CD38, CD56, CD138, cLambda, sIgM, and cIgM, but not CD19, and were classified as abnormal monoclonal plasma cells. We performed immunofixation electrophoresis, which indicated an M protein level of 16.75364 g/L. The FISH results indicated that the tumour cells were *IGH/FGFR3* gene locus fusion-positive and *TP53* gene locus amplification-positive; other test results were negative. The chemotherapy regimen was adjusted to VRD (bortezomib 1.3 mg/m^2 d1/4/8/11, lenalidomide 25 mg d1-14, and dexamethasone 20 mg d1/2/8/9/15/16/22/23).

The maximum depth of response was VGPR, and to date, there has been no disease recurrence or progression. It has been over 64 months since diagnosis. Additionally, she had not received other treatment other than chemotherapy specified by MM before, and has experienced no adverse events such as arrhythmia, liver and kidney damage, or thrombosis. After starting the VRD-based regimen, the patient's clinical manifestations and laboratory results were significantly improved compared with those before treatment (Fig. 3), as were the anaemia and bone and low back pain. The laboratory test results after treatment were as follows: albumin, 42.58 g/L; globulin, 28.28 g/L; M protein, 9.92 g/L; IgG, 17 g/L; IgA, 0.9 g/L; IgM, 0.57 g/L; and haemoglobin, 120 g/L.

The patient consented in writing to the publication of the case report.

(Cell Population Proportion: Lymphocyte(Green): 23.3%, Monocyte(Purple): 6.8%, Granulocyte(Blue): 53.3%, Blast Region(Sky Blue): 3.4%, Abnormal cell(Red): 2.2%, Erythroblast(Gray): 11.0%. Antigens examined in this test: HLA-DR、CD2、CD3、CD4、CD5、CD7、CD8、CD10、CD11b、CD11c、CD13、CD14、CD15、CD16、CD19、CD20、CD22、CD23、CD25、CD33、CD34、CD36、CD38、CD56、CD64、CD71、CD103、CD117、FMC-7、cCD3、cIgM、sIgM、cKappa、cLambda、Kappa、Lambda、

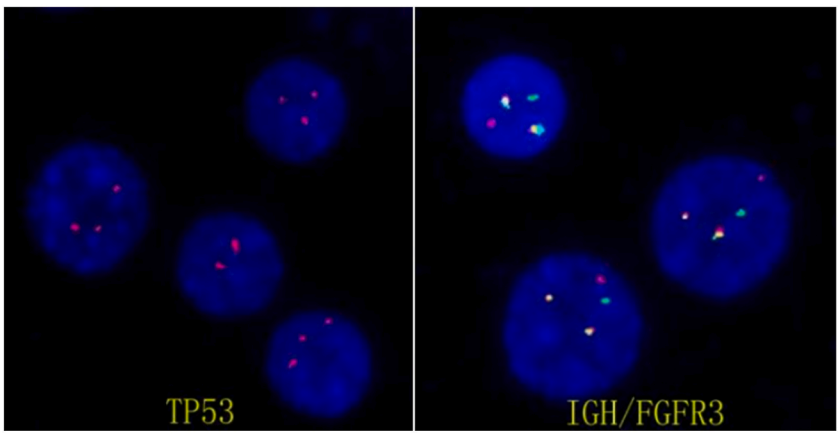

Fig. 2. FISH results showed abnormal cytogenetic karyotypes: TP53 locus amplification (17p gain)[Fig.2(a)] and IGH/FGFR3 locus fusion [t(4; 14)] [Fig.2(b)]. FISH: ; IGH: ; FGFR3.

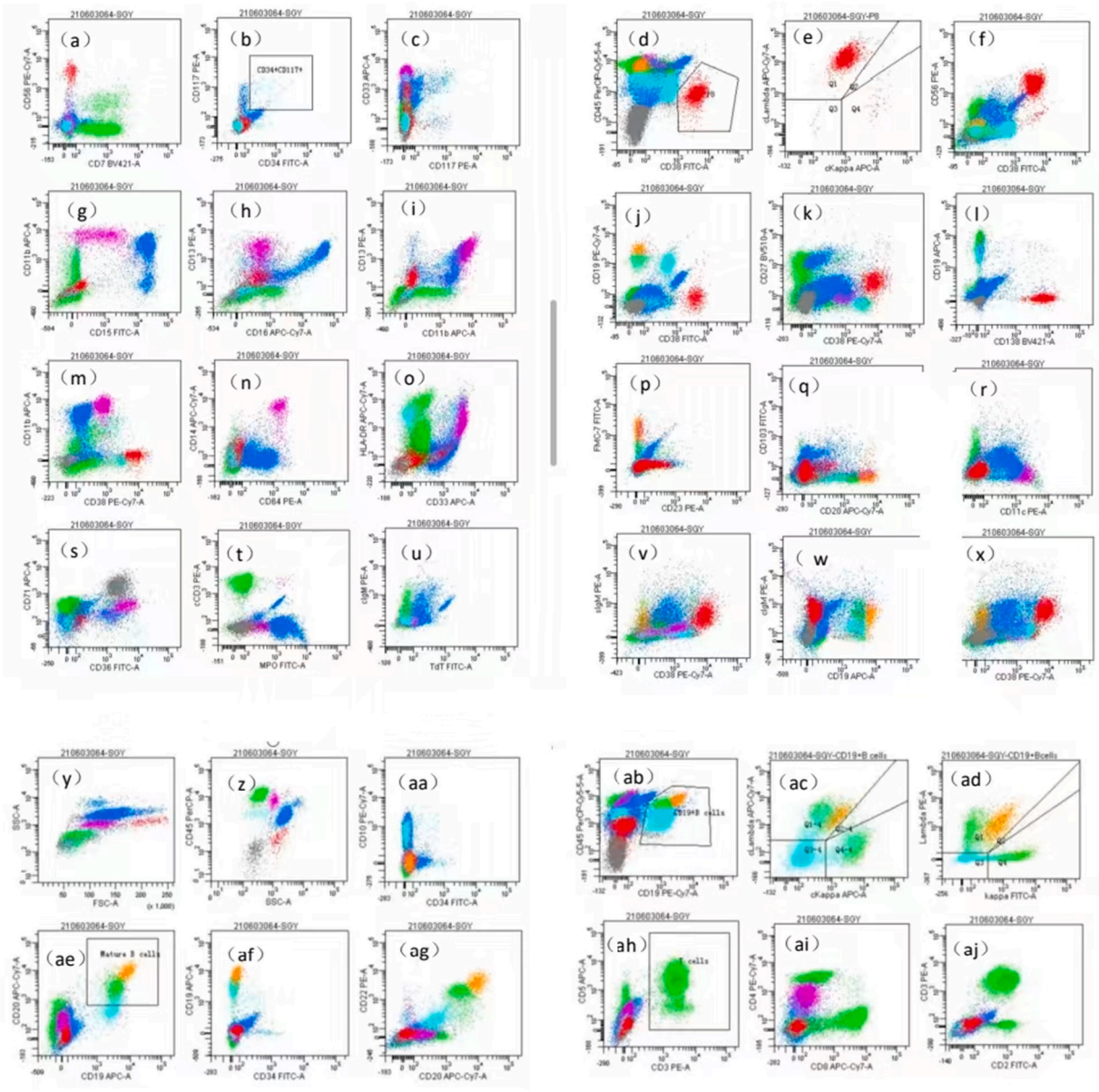

Fig. 3. Immunophenotyping of haematologic subpopulations by flow cytometry post-treatment.

MPO、TdT、CD45[Fig.3(a)-Fig.3(aj)]. Instrument: Flow cytometer.)

3. Discussion

With the advancement of detection technology and increased understanding of various genetic lesions, cytogenetic karyotyping has become an important factor in the diagnosis and prognostic evaluation of haematological diseases and tumours. Patients with MM have abnormal cytogenetic karyotypes that provide important evidence for prognostic assessment [13]. Therefore, the analysis of new cytogenetic abnormalities is important for disease prognosis.

Genetic abnormalities in MM cells are intrinsically critical determinants of tumour characteristics, as they reflect the natural history of the disease and drug sensitivity. Hanamura et al. summarised the high-risk cytogenetic karyotypes associated with MM, with cytogenetic abnormalities such as t(4; 14), t(14; 16), t(14; 20), gain/amp (1q21), del(1p), and del(17p) being the most widely accepted predictors of poor prognosis in MM; coexisting high-risk cytogenetic abnormalities are often associated with worse prognosis [14].

Immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies are used in clinical practice to treat MM. The combination of IMiDs + PIs can help rapidly reduce the number of tumour cells, reduce the tumour burden, control

symptoms, and improve clinical efficacy in patients with MM. Roussel et al. [15] used VRD to treat elderly patients with MM and observed good response and tolerability. However, the clinical benefit for MM patients with high-risk cytogenetic karyotypes is not satisfactory, and they are prone to recurrence or adverse reactions that seriously affect clinical efficacy and prognosis [11,16]. One clinical trial analysed the clinical benefit of ituximab to that of carfilzomib plus dexamethasone in patients with high-risk cytogenetics and found PFS improved in patients with a t(4; 14) karyotype (HR 0.724; 95% CI: 0.361–1.451), whereas the PFS benefit was less pronounced in patients with a del(17p) karyotype [17]. Aberrant cytogenetics may be a promising therapeutic target for MM; For example, amp(1q21) is associated with increased sensitivity to MCL-1 inhibitors [18]. Additionally, a previous study found that MM cells with t(4; 14) translocations are sensitive to BCL2 inhibition, compared to cells without this translocation, and the expression of the anti-apoptotic protein BCL2 is relatively high in MM cells [5,17].

The presence of del(17p) and/or *TP53* mutations is an independent prognostic factor for chronic lymphocytic leukaemia (CLL) and is associated with a poor prognosis [19]; del(17p) and *TP53* mutations can predict resistance to chemoimmunotherapy and poor survival in patients with CLL, whereas 17p gain is a karyotype associated with a good prognosis in CLL [20]. Since both MM and CLL are caused by plasma cell abnormalities, we believe that 17p gain in MM is worth discussing, as it has not been documented in the literature. In this case, the VRD regimen alone led to good disease control in a patient with 17p gain and t(4; 14) translocation. Patients with MM with t(4; 14) have a median overall survival (OS) of less than 1 year; however, our patient has been progression-free for more than 3 years and has survived for more than 5 years since diagnosis [21]. Therefore, 17p gain may be a cytogenetic karyotype that suggests a good prognosis for patients with MM, even if it appears alongside t(4; 14). Early analysis of chromosomal karyotypes in patients with MM using cytogenetic karyotyping can help determine the degree of clinical benefit, risk, and prognosis. However, this is only a case report of a single patient, not the result of statistical analysis of large sample data; therefore, the results may not be representative of all patients with MM. The collection of more clinical sample data is needed.

4. Conclusion

17p gain is an abnormal karyotype in MM. This patient with MM with 17p gain achieved a PFS over 3 years and an OS over 5 years, suggesting that 17p gain may be a cytogenetic karyotype predictive of a good prognosis in MM. The relationship between 17p gain and MM prognosis has received little attention, and the case described here is expected to trigger new thinking and supplement the prognostic analysis of patients with MM.

Ethics approval and consent to participate

The patient provided informed consent to participate in the study.

Data availability statement

Data included in article/supp. material/referenced in article. All data underlying the findings are presented in the article.

Funding

This study was supported by the “Taishan Scholar Young Expert” Project Special Fund (tsqn202211351) and National Natural Science Foundation of China (No. 82174181).

CRediT authorship contribution statement

Xinyu Tang: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Ruirong Xu:** Writing – review & editing, Supervision, Methodology. **Wei Zheng:** Validation, Data curation. **Yanfeng Zhou:** Methodology, Conceptualization. **Siyuan Cui:** Writing – review & editing, Methodology. **Yan Wang:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interestsYan Wang reports financial support was provided by National Natural Science Foundation of China. Yan Wang reports financial support was provided by Shandong Provincial Health Commision. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28950.

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