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CASE REPORTS

t(11;14) multiple myeloma patient: minimal residual disease after 10 years of follow-up - a case report

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Authors' contributions: SD, JC and LG wrote the manuscript. JC and AS carried out cytogenetic analysis. JC, AS and SM carried out MRD assays. LG treated and followed the patient. PAV and OL contributed to imaging analysis. All authors contributed to the final version of the manuscript.

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Key points: This t(11;14) myeloma patient had bone marrow NGS based increased MRD positivity for more than 10 years without the need for resuming treatment.

Over the past two decades, the emergence of new therapeutic approaches has revolutionized the care of patients suffering from multiple myeloma (MM). However, despite overall improvements in life expectancy, it is still, to this day, an incurable disease in which significant disparities in treatment response remain (e.g., ranging from few months to several decades).^{1,2} Therefore, being able to accurately predict patient outcomes and identify patient relapse without delay is crucial. In 2016, the *International Myeloma Working Group* (IMWG) has included the concept of minimal residual disease (MRD) as one of the response criteria, among others, to evaluate the number of malignant plasma cells (PCs) remaining during and after therapy demonstrating treatment effectiveness especially for patients achieving complete response.^{3,4} Since then, its prognostic role has been well established in various studies^{5,6}. Two years later, in 2018, *Perrot et al.*⁷ demonstrated that an undetectable MRD below 10^{-6} at the start and after maintenance therapy was associated with better progression-free survival (PFS) and overall survival (OS) regardless of treatment regimen, International Staging System (ISS) and 17p deletion, t(4;14) or t(14;16) status. However, despite those promising results, the role of MRD as a surrogate marker enabling early treatment changes according to its value is still under investigation with undetectable MRD patients still relapsing early whereas, on the contrary some patients have detectable MRD but favorable outcomes.^{4,5,8,9} This is particularly true for patients harboring a t(11;14) translocation. Initially associated with a neutral impact on the course of the disease, its prognostic role on patient outcome remains controversial to this date because of conflicting data depending on treatment used, other associated abnormalities or even other diseases characteristics.¹⁰ Thus, it seems that t(11;14) constitutes a much more complex group than it first appeared, that cannot be ignored, as it represents 15-20% of newly diagnosed MM patients. In recent studies, a slower treatment response tends to be depicted¹¹⁻¹³ in those patients objectified by a longer time to reach undetectable MRD than in non-t(11;14) patients without impacting PFS and OS parameters. For instance, *Liu et al.* highlighted in their study a difference of approximately 5 months to achieve a negative MRD ($<10^{-5}$) between standard risk patients (approximately 4 months to obtain a negative-MRD) and patients with a unique abnormality of interest being t(11;14) (approximately 9 months).¹³ In a similar way, MIDAS first published results showed that only 24% of the patients with t(11;14) had MRD $<10^{-6}$ after induction against 59% for non-t(11;14) regardless of the trial group meanwhile before maintenance therapy 63% of the t(11;14) patients were MRD-negative (against 78%), showing a delayed response.¹¹

Here, we report the case of a 55-year-old woman diagnosed in December 2013 with a light-chain MM following the onset of severe lumbar pain appearing by uprooting a plant in May 2013. The patient gave informed consent for the use of laboratory results and clinical data for research purposes according to the Declaration of Helsinki; the Toulouse Ethics Committee approved the study. Informed consent was obtained from the patient. Diagnosis has been made in the presence of 28% of malignant PCs in bone marrow sample. A mild anemia at 10.5 g/dL (12-16 g/dL) was also found at diagnosis. Blood creatinine and calcium were included into physiological intervals. Serum protein electrophoresis showed no M-spike, only a hypo-gammaglobulinemia at 4.3 g/L (6.9-15 g/L). However, an increased concentration of kappa (κ) free light chain at 1,157 mg/L (3.3-19.4 mg/L) was highlighted whereas lambda (λ) free light chain concentration was below 0.5 mg/L (5.7-26.3 mg/L). Lastly, to support diagnosis, multiple bone lesions were visualized on X-rays. Moreover, bone compressions and diffuse bone reshaping were seen on magnetic resonance imaging. Thus, the diagnosis of κ light-chain MM was established and an ISS of 1 was calculated based on

blood albumin concentration of 36.4 g/L (35-53 g/L) and β 2-microglobuline of 2.34 mg/L (0.8-2.2 mg/L). At that time, the cytogenetic risk was assessed by FISH (Fluorescence In Situ Hybridization) on CD138 sorted bone marrow plasma cells: no del(17p), t(4;14), t(14;16) were found, only a t(11;14) in 46% of sorted plasma cells was highlighted. As a result, the patient was classified as standard cytogenetic risk.

Following that diagnosis, patient underwent 4 cycles of bortezomib-thalidomide-dexamethasone (VTd), intensification with high-dose melphalan, an autologous hematopoietic stem cell transplant (ASCT) on May 16th, 2014, and, finally, 2 further VTd consolidation cycles without maintenance treatment. Afterwards, a complete response to the treatment was achieved as defined by the 2016 standard IMWG response criteria.³ As a result, the patient benefited for a close monitoring including bone marrow, blood and imaging follow-up (Figure 1 and Table 1) without any further treatment. All MRD assessments were done by next generation sequencing (NGS) using Clonoseq Adaptive platform. The first MRD assessment was done in post consolidation and was evaluated at 2.6×10^{-6} . Until 2016 (two years from end of treatment), patient had MRD values between 10^{-6} and 10^{-5} . Yet, since 2017, we are seeing a gradual increase in her MRD status until reaching 4.8×10^{-2} in the absence of other positive bone marrow, blood and bone imaging parameters, at first. However, more recently, κ free light chains have begun to gradually reappear (≥ 10 mg/L) and display an abnormal ratio starting in September 2020 while medullar PCs have risen above 5% in bone marrow around March 2021, meeting criteria to a biological relapse. Yet, to this date none of the following essential criteria for clinical relapse according to the 2016 standard IMWG response criteria have been experienced by the patient:

- “Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder,
- Development of new soft tissue plasmacytomas or bone lesions,
- Increase in the size of existing plasmacytomas or bone lesions of 50% (and ≥ 1 cm),
- Hypercalcemia (>11 mg/dL),
- Decrease in haemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions,
- Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma,
- Hyperviscosity related to serum paraprotein.”³

Consequently, the patient has been maintained in therapeutic withdrawal until now.

While recent data suggest that patients with t(11;14) respond much more slowly (but as well or better) to treatment than others, this case suggests that these patients may remain MRD positive without relapsing, and that the kinetics of MRD reappearance are also extremely slow and progressive before relapse. This case report should also be considered in parallel with the work of *Burgos et al.* on monoclonal gammopathy of undetermined significance(MGUS)-like phenotype in MM patients which was found to predict a more favorable prognosis compared to intermediate or MM-like phenotypes. This MGUS-like phenotype, obtained using an open-access calculator, translates into improved PFS and OS regardless of MRD negativity or persistence and treatment response.¹⁴ Unfortunately, in that case no flow cytometry was required at time of diagnosis, so we were unable to determine the phenotype status of our patient. Therefore, all these observations raise numerous questions especially in the context of new clinical trials using sustained MRD to adjust treatment as, for instance, in MIDAS, PERSEUS, GEM2014MAIN, RADAR, S1803 trials and

many others. Regarding PERSEUS study, daratumumab-bortezomib-lenalidomide-dexamethasone (D-VRd) regimen was compared to bortezomib-lenalidomide-dexamethasone (VRd) combination in induction and consolidation followed by either D-R or R alone respectively in eligible ASCT MM patients. After at least 24 months of maintenance, it was foreseen that daratumumab could be discontinued if patients had undetectable sustained MRD at a sensitivity threshold of 10^{-5} or lower, while maintaining lenalidomide alone. Conversely, daratumumab could be resumed upon loss of MRD negativity at a sensitivity threshold of 10^{-4} or higher.¹⁵ Similarly, in the MIDAS study, treatment intensiveness was stratified according to MRD results after induction. In the first published results of this study, it is important to point that the more intensive treatment groups are particularly enriched in t(11;14) patients. Thus, future results of MIDAS study as well as further investigations will be needed to determine the place of t(11;14) patients within ongoing clinical trials. Should MRD be maintained as an unequivocal indication to discontinue, resume, or select a particular treatment, especially when emerging evidence suggests it may not always correlate with poorer PFS or OS for this specific group? Perhaps what is needed is a more global assessment of patient's treatment response⁹ alongside with MRD, including cytogenetic and/or immune features, MGUS-like profiles, imaging and/or clinical markers. Further studies will be needed to clarify those findings.

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Table 1: Biological parameters of the patient over the past 10 years. *The following table combines bone marrow, blood and bone imaging results at the corresponding points.*

Collection date	Nov 17, 2014	May 11, 2015	Dec 21, 2015	June 20, 2016	Jan 05, 2017	Mar 21, 2018	Nov 12, 2018	Mar 22, 2021	Apr 14, 2022	May 04, 2023	Jan 06, 2025	June 16, 2025
BM plasmacytosis (%)	Normal	1	-	2	1	2	4	8	12	8	11	-
BM phenotype:		0.1	-	-	Non	-	0.35	0.9	2	2	3	-
PCs% (clonal PCs%)	-	(70% κ)	-	-	clonal	-	(66% κ)	(86% κ)	(91% κ)	(93% κ)	(93% κ)	-
SPEP	Negative	Negative	-	Negative	-	-	Negative	Negative	-	Negative	Negative	-
sIF	Negative	Negative	-	-	-	-	Negative	Negative	-	Negative	Negative	Negative
IgG, IgA, IgM	-	Normal	Normal	-	-	Normal	Normal	Normal	Normal	Normal	-	Normal
κ free light chain (mg/L)	<7	<6	8	8	9	11	13	40	81	120	140	206
λ free light chain (mg/L)	<4	<4	10	9	10	11	11	7.5	9	8	9.5	5.5
sFLC ratio	-	-	0.8	0.9	0.9	1	1.18	5	9	15	15	37
dFLC (mg/L)	-	-	-	-	-	-	2	32.5	72	112	130.5	201
β2-microglobuline (mg/L)	-	-	1.1	-	-	1.5	1.1	1.42	1.7	1.32	1.11	1.4
Albuminemia (g/L)	-	-	43	-	-	46	39	41	40	46	42	38.6
LDH (IU/L)	-	-	-	-	-	362	322	245	213	218	197	217
Creatininemia (μM)	-	63	65	66	-	69	61	50	53	53	54	55
24h proteinuria (g/24h)	-	-	0.02	-	-	-	-	0.06	0.06	0.09	0.06	0.06
uIF (Bence Jones proteinuria search)	-	Negative	-	-	-	-	-	Negative	-	Negative	Negative	Negative
FDG-PET/CT	-	-	Normal	-	Normal	-	Normal Salt and pepper without focal lesions	-	-	-	-	-
Whole body MRI	-	-	Stable	-	-	-	-	-	-	-	-	-
PET-MRI	-	-	-	-	-	-	-	Stable	Few focal lesions, stable, hypermetabolism, salt and pepper	Stable	Stable	-

BM: bone marrow; **PCs:** plasma cells; **SPEP:** serum protein electrophoresis; **sIF:** serum immunofixation; **κ free light chain:** kappa free light chain (normal values: 3.3-19.4 mg/L); **λ free light chain:** lambda free light chain (normal values: 5.7-26.3 mg/L); **sFLC ratio:** serum free light chains ratio = κ/λ (normal values: 0.26-3.60); **dFLC:** difference in free light chains = κ-λ; **β2-microglobuline** (normal values: 0.8-2.2 mg/L); **Albuminemia** (normal values: 35-53 g/L); **LDH:** lactate dehydrogenase (normal values: 135-215 IU/L); **Creatininemia** (normal values: 45-84 μM); **24h proteinuria** (normal values: <0.15 g/24h); **uIF:** urine immunofixation; **FDG-PET/CT:** ¹⁸fluoro-deoxyglucose-positron emission tomography/computed tomography; **MRI:** magnetic resonance imaging; **PET-MRI:** positron emission tomography-MRI.

Figure Legends

Figure 1: MRD and free light chain follow-up from 2014 to 2025 performed respectively at Toulouse Unit for Genomics in Myeloma and at Greater Paris University Hospitals (AP-HP). MRD, on the left side of the graph is represented on a logarithmic scale, whereas κ free light chain, on the right side of the graph is represented on a non-logarithmic scale in mg/L. ASCT: autologous hematopoietic stem cell transplant.

