Annals of Hematology (2019) 98:2463–2465
https://doi.org/10.1007/s00277-019-03743-6

LETTER TO THE EDITOR

Multiple myeloma with *IGH-FGFR3* rearrangement progressing as testicular plasmacytoma during carfilzomib treatment

Nobuhiko Nakamura[1] · Dai Maruyama[1] · Akiko Miyagi Maeshima[2] · Yo Saito[1] · Takahiro Fujino[1] · Yuta Ito[1] · Shunsuke Hatta[1] · Shinichi Makita[1] · Suguru Fukuhara[1] · Wataru Munakata[1] · Tatsuya Suzuki[1] · Hiroyuki Fujimoto[3] · Koji Izutsu[1]

Received: 6 May 2019 / Accepted: 15 June 2019 / Published online: 25 June 2019

Dear Editor,

Multiple myeloma (MM) is a heterogeneous hematological malignancy with the clonal proliferation of plasma cells. Although MM remains incurable, treatment strategies have been improved by developing new agents and the overall survival of MM patients has significantly increased in the last decades [1]. Extramedullary spread of MM may occur either at diagnosis or during the disease course, and testis involvement is rare. We report an MM patient with *IGH-FGFR3* rearrangement progressing as a testicular plasmacytoma during carfilzomib (CFZ) treatment.

A 72-year-old man was diagnosed with MM with *IGH-FGFR3* rearrangement (IgG-λ, stage 2 according to the International Staging System [2]) 8 years ago. He received 3 cycles of bortezomib and dexamethasone induction therapy, and high-dose melphalan followed by autologous stem cell transplantation. He achieved very good partial response (VGPR) and was followed-up without any treatment. Four years later, he had significant paraprotein relapse without any other symptoms and received CFZ, lenalidomide, and dexamethasone (CLd) therapy. After 9 cycles of CLd therapy, he achieved VGPR again. After 1 year of CLd therapy, we stopped lenalidomide because of thrombocytopenia. Although he maintained VGPR for another year, he felt left-testicular swelling and underwent left orchiectomy. Histopathology revealed infiltration of plasmacytoma in the testis, which was positive for *IGH-FGFR3* by fluorescent in situ hybridization (FISH) analysis (Fig. 1). We confirmed the absence of M-protein in the serum and urine, and the percentage of plasma cells in the bone marrow was 0.2% and clonality of plasma cells was not detected. *IGH-FGFR3* rearrangement was not detected in bone marrow by FISH analysis. There was no other plasmacytoma by FDG-PET/CT scan. Three months after the operation, disease progression was not observed and no additional treatment was given.

Solitary extramedullary plasmacytomas are plasma cell tumors that arise outside of the bone marrow and are most often located in the head and neck region, mainly in the upper aerodigestive tract [3]. The incidence of solitary plasmacytoma during follow-up of MM is 6% [4]. Testicular plasmacytomas are rare, accounting for only 1.3% of all extramedullary plasmacytomas [3] and 0.03 to 0.1% of all testicular tumors [5]. It is unclear whether testicular involvement by plasmacytoma is associated with a risk of central nervous system relapse like diffuse large B cell lymphoma [6]. Although testicular plasmacytoma has been reported, the relationship with cytogenetic risk or new agents has not been reported.

Cytogenetic abnormalities are powerful prognostic factors in MM [7]. Rearrangement of the *FGFR3* and *IGH* genes is designated as t(4;14), and it has been observed in up to 15% of MM patients and is associated with poor prognosis [8]. Importantly, bortezomib improves the negative prognostic impact of t(4;14) [9]. Carfilzomib is an epoxyketone proteasome inhibitor that selectively and irreversibly binds the constitutive proteasome and immunoproteasome. The phase 3 study ASPIRE, which compared CLd with lenalidomide and dexamethasone (Ld), demonstrated CLd to have a favorable benefit-risk profile compared with Ld, regardless of baseline cytogenetic risk status, in patients with relapsed/refractory MM [10]. In our patient, CLd therapy was effective for MM with *IgH-FGFR3* rearrangement and VGPR was maintained

✉ Dai Maruyama
dmaruyam@ncc.go.jp

[1] Department of Hematology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

[2] Department of Pathology and Clinical Laboratory, National Cancer Center Hospital, Tokyo, Japan

[3] Department of Urology, National Cancer Center Hospital, Tokyo, Japan

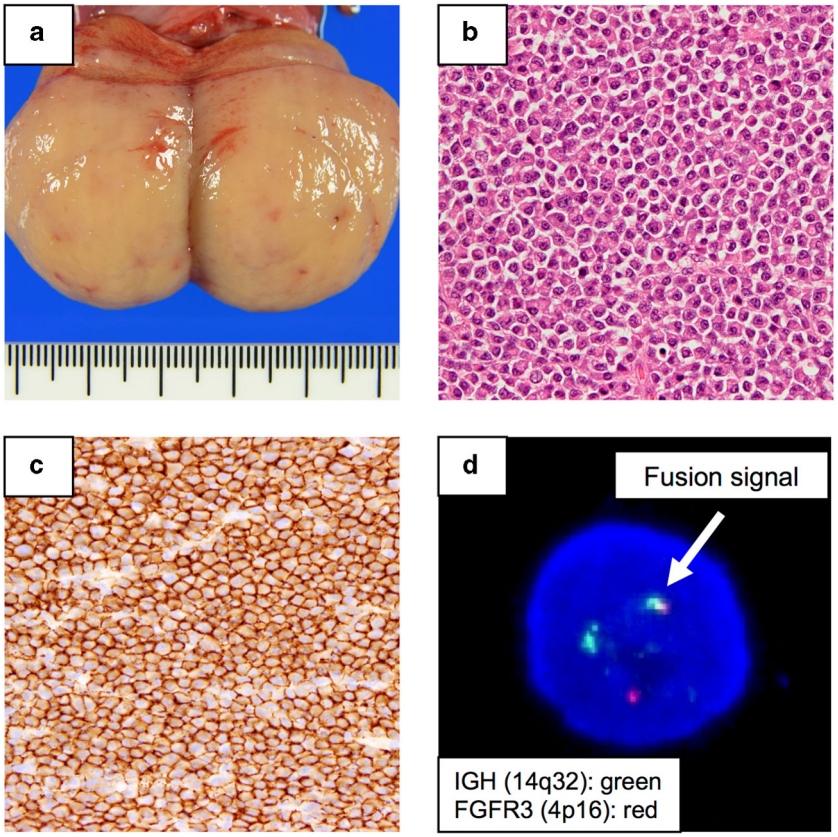

Fig. 1 **a** The extracted specimen of the left testis. **b** Hematoxylin and eosin staining showed diffuse infiltration of plasma cells in the testis (× 400). **c** The plasma cells were positive for CD138 by immunohistochemistry (× 400). **d** Fusion signal of *IGH-FGFR3* FISH analysis of testicular tumor was positive

for 2 years. It is necessary to consider the possibility of progression as extramedullary plasmacytoma even if proteasome inhibitors, such as CFZ, were effective in terms of M-protein and a rare location, such as the testis, is involved in high-risk MM patients with *IGH-FGFR3* rearrangement.

Compliance with ethical standards

Conflict of interest Dai Maruyama has received honoraria and research funding from Janssen, Celgene, Ono, and Bristol-Myers Squibb Japan.

Informed consent Informed consent to publish case details was obtained from the patient.

References

1. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE (2017) Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv 1:282–287. https://doi.org/10.1182/bloodadvances.2016002493
2. Sonneveld P, Westin J, Shimizu K, Morgan G, Greipp PR, Durie BGM, Ludwig H, Avet-Loiseau H, Kyle RA, Powles R, Shustik C, Child JA, Bladé J, Turesson I, Lahuerta JJ, Barlogie B, Miguel JS, Boccadoro M, Crowley JJ, Tosi P (2005) International staging system for multiple myeloma. J Clin Oncol 23:3412–3420. https://doi.org/10.1200/jco.2005.04.242
3. Alexiou C, Kau RJ, Dietzfelbinger H, Kremer M, Spiess JC, Schratzenstaller B, Arnold W (1999) Extramedullary plasmacytoma: tumor occurrence and therapeutic concepts. Cancer 85:2305–2314
4. Lazzarino M, Pica G, Varettoni M, Mangiacavalli S, Corso A, Pascutto C (2009) Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients. Ann Oncol 21:325–330. https://doi.org/10.1093/annonc/mdp329
5. Rosenberg S, Shapur N, Gofrit O, Or R (2010) Plasmacytoma of the testis in a patient with previous multiple myeloma: is the testis a sanctuary site? J Clin Oncol 28:e456–e458. https://doi.org/10.1200/jco.2009.27.6519
6. Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U, Klasa R, Ozsahin M, Mead GM, Gianni MA, Cortelazzo S, Ferreri AJM, Ambrosetti A, Martelli M, Thiéblemont C, Moreno HG, Pinotti G, Martinelli G, Mozzana R, Grisanti S, Provencio M, Balzarotti M, Laveder F, Oltean G, Callea V, Roy P, Cavalli F, Gospodarowicz MK (2003) Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the international extranodal lymphoma study group. J Clin Oncol 21:20–27. https://doi.org/10.1200/JCO.2003.11.141
7. Sonneveld P, Lonial S, Usmani S, Siegel D, Anderson KC, Van De Donk NWCJ, Einsele H, Blad J, Palumbo A, Orlowski R (2017) Perspectives treatment of multiple myeloma with high-risk cytogenetics : a consensus of the international myeloma working group. Blood 127:2955–2963. https://doi.org/10.1182/blood-2016-01-631200.BLOOD

8. Keats JJ, Reiman T, Maxwell CA, Taylor BJ, Larratt LM, Mant MJ, Belch AR, Pilarski LM (2003) In multiple myeloma, t(4;14)(p16;q32) is an adverse prognostic factor irrespective of FGFR3 expression. Blood 101:1520–1529. https://doi.org/10.1182/blood-2002-06-1675
9. Avet-Loiseau H, Leleu X, Roussel M, Moreau P, Guerin-Charbonnel C, Caillot D, Marit G, Benboubker L, Voillat L, Mathiot C, Kolb B, Macro M, Campion L, Wetterwald M, Stoppa A-M, Hulin C, Facon T, Attal M, Minvielle S, Harousseau J-L (2010) Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). J Clin Oncol 28:4630–4634. https://doi.org/10.1200/JCO.2010.28.3945
10. Avet-Loiseau H, Fonseca R, Siegel D, Dimopoulos MA, Špička I, Masszi T, Hájek R, Rosiñol L, Goranova-Marinova V, Mihaylov G, Maisnar V, Mateos M-V, Wang M, Niesvizky R, Oriol A, Jakubowiak A, Minarik J, Palumbo A, Bensinger W, Kukreti V, Ben-Yehuda D, Stewart AK, Obreja M, Moreau P (2016) Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma. Blood 128:1174–1180. https://doi.org/10.1182/blood-2016-03-707596