Cytogenetic Study and Analysis of Protein Expression in Plasma Cell Myeloma with t(11;14)(q13;q32): Absence of BCL6 and SOX11, and Infrequent Expression of CD20 and PAX5

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The t(11;14)(q13;q32) translocation is the most common chromosomal translocation in plasma cell myeloma (PCM), but the cytogenetic and immunophenotypic features of PCM with t(11;14)(q13;q32) remain to be fully elucidated. To address the issue, we retrospectively analyzed 21 newly diagnosed PCM patients with the t(11;14)(q13;q32) translocation in our institute. CD20 is a B-cell-specific transmembrane protein that is the topic of much focus as a potential target in immunotherapy. We observed a low incidence of CD20 expression (2 of 21 patients, 11%), although the expression of CD20 was previously reported to be associated with t(11;14)(q13;q32). PAX5 is an essential transcriptional factor involved in B-cell development and commitment, and is down-regulated upon plasma cell differentiation. We observed one patient (6%) with expression of PAX5. The expression of CD19, CD56, and CD138 was detected in one (0.7%), nine (60%), and 13 patients (87%), respectively. Cyclin D1, CD38, and BCL2 were detected in all patients; on the other hand, neither BCL6 nor SOX11 was detected in any of the evaluated patients. Our results suggest the absence of BCL6 and SOX11 expression, and infrequent expression of CD20, PAX5, and CD56 in PCM with t(11;14)(q13;q32), in contrast to the findings of earlier reports. [J Clin Exp Hematop 55(3) : 137-143, 2015]

Keywords: CD20, PAX5, SOX11, BCL6, CD56

INTRODUCTION

Plasma cell myeloma (PCM) is a hematologic neoplasm characterized by monoclonal proliferation of plasma cells in the bone marrow. Nearly half of all patients with PCM carry chromosomal translocations involving the immunoglobulin heavy chain (IGH) locus at 14q32.1 The t(11;14)(q13;q32) translocation is the most common IGH translocation in PCM, with a prevalence of approximately 15%.1 As a result of this translocation, the coding region of cyclin D1 (CCND1) on 11q13 is juxtaposed to the transcriptionally active enhancers of IGH, resulting in upregulated expression of CCND1.2 CD20 is a B-cell-specific transmembrane protein with four membrane-spanning domains.3 Although the exact function of CD20 is not fully elucidated, it is believed that CD20 is involved in B-cell activation and proliferation, and regulation of transmembrane calcium transport.4 CD20 is expressed in committed B-cells throughout their development, but is lost upon differentiation to plasma cells.5 However, Robillard et al. reported that CD20 was expressed in 12 (18%) of 66 PCM patients.5 Interestingly, they showed a significant correlation between immunophenotype and genotype; the expression of CD20 was strongly associated with t(11;14)(q13;q32) (10 of 12 patients, 88%). On the other hand, recent studies reported lower correlation between the expression of CD20 and t(11;14)(q13;q32).6,7 PAX5 is a transcriptional factor that is expressed in B-cells and the nervous system.8 In B-cells, the expression of PAX5 is initiated in the pre-pro-B cells, maintained through
out subsequent stages of B-cell development, and is silenced upon plasma cell differentiation. In PAX5-deficient mice, B-cell development is arrested at a very early stage. PAX5 activates B-cell specific genes, including Ebf1, CD19, and CD79a, and represses lineage-inappropriate genes, including Notch1, Csf1r, and Flt3. Thus, PAX5 plays an essential role in B-cell development and commitment. Concurrently, PAX5 represses both Xbp1 and Blimp1, which are required for plasma cell differentiation. Hence, down-regulation of PAX5 expression is required for differentiation to plasma cells, and consequently, PAX5 is not expressed in plasma cells. PCM cells have been assumed to not express PAX5 by analogy with normal plasma cells. In addition, Proulx et al. reported that PAX5 overexpression induces apoptosis in PCM cell lines. However, Torlakovic et al. reported that 2 of 39 (5%) PCM patients showed unequivocal focal expression of PAX5, and two more patients were border-line positive. Notably, these four patients also exhibited weak expression of CD20.

Accordingly, the expression patterns of CD20 and PAX5 in PCM with t(11;14)(q13;q32) remain unclear. To clarify the characteristics of PCM cells with t(11;14)(q13;q32), we retrospectively analyzed newly diagnosed PCM patients in our institute.

PATIENTS AND METHODS

Patients

We retrospectively reviewed 21 PCM patients with t(11;14)(q13;q32) who were treated at our institute between May 2003 and October 2013. The diagnosis of PCM was made according to the 2008 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Chromosome analysis and fluorescence in situ hybridization (FISH) were used to detect t(11;14)(q13;q32). The study protocol was approved by the Institutional Review Board of St. Marianna University School of Medicine.

Chromosome analysis and FISH

Chromosome analysis of aspirated bone marrow cells was performed using a conventional G-bandning technique. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (2013). FISH was performed on the same aspirated bone marrow cells. FISH probes included Vysis LSI IGH/CCND1 (Abbot Laboratories, North Chicago, IL, USA) for t(11;14)(q13;q32), Vysis D13S319 (Abbot Laboratories) for chromosome 13 abnormalities (-13/13q-), and Vysis TP53/CEP17 (FISH Probe Kit; Abbot Laboratories) for detection of TP53 deletions.

RESULTS

Patient characteristics

Patient characteristics are summarized in Table 1. The median age at diagnosis was 69 years with a slight predominance of females (57%). Monoclonal serum paraprotein was detected in 20 of 21 patients with the following subtypes; IgG in seven patients (33%), IgA in five (24%), and light chain only (Bence Jones protein type, BJP type) in eight (38%). Only one patient had non-secretory PCM. The type of light chain was κ in seven patients (33%) and λ in 14 (67%). Nine patients (43%) were classified as stage III according to the International Staging System. Laboratory data of all patients are shown in Table 2. The median percentage of plasma cells was 58.9%.

Chromosome analysis and FISH

Of the 21 patients, 18 (86%) showed normal karyotype, but one patient showed the following complex chromosome abnormality in addition to t(11;14)(q13;q32): 47,XY,der(1)ins(1;14)(p32;q11.2q32),i(1)(q10),del(8)(p?),del(11)(q13),-14,der(14)t(11;14)(q11.2;q13.33)46,XY[18]. FISH revealed the fusion signals of IGH and CCND1 in the patients with normal karyotype. Abnormalities of -13/13q- were detected in six patients (UPN 2, 5, 6, 11, 16, and 21) (38%). On the
other hand, the deletion of TP53 was not detected in any of the evaluated patients.

**Flow cytometry**

The results of flow cytometry are shown in Table 3. CD19 was positive in only one patient (0.1%), CD20 in nine (60%), and CD138 in 13 (87%). The immunophenotypes of the PCM cells were classified as immature, intermediate, or mature, as defined by Huang et al.\(^{17}\) The immature phenotype of PCM cells (MPC1 - /CD49e - ) was observed in three patients (20%), the intermediate phenotype (MPC1 + /CD49e - ) in seven (50%), and the mature phenotype (MPC1 + /CD49e + ) in five (30%).

**Immunohistochemical analysis**

The results of immunohistochemical analysis are shown in Table 4. Strong nuclear positivity of CCND1 was observed in all of the evaluated patients. Both CD38 and BCL2 were also positive in all evaluated patients. CD20 was positive in two patients (11%) (Fig. 2c, 2f), and CD20 expression in these patients was also detected by flow cytometry. May-Grünwald-Giemsa-stained PCM cells exhibited a lymphoplasmacytic cell morphology, as defined by Goasguen et al.\(^{18}\) (Fig. 2a, 2d). PAX5 was positive in only one patient (0.06%), as discussed in our previous report (UPN3).\(^{19}\) The karyotype of this patient was normal at diagnosis, but t(9;14)(p13;q32), a complex variant translocation of t(11;14)(q13;q32) in PCM with t(11;14)(q13;q32)

| UPN | Hb (g/dL) | WBC (10^9/L) | M protein | ISS |
|-----|-----------|--------------|-----------|-----|
| 1   | 10.3      | 3.5          | IgG        | k   |
| 2   | 10.7      | 5.4          | IgG        | k   |
| 3   | 11.6      | 4.9          | IgG        | k   |
| 4   | 12.6      | 8.3          | IgG        | k   |
| 5   | 10.2      | 4.5          | IgG        | k   |
| 6   | 9.2       | 3.2          | IgG        | k   |
| 7   | 10.2      | 5.8          | IgG        | k   |
| 8   | 8.4       | 7.2          | IgG        | k   |
| 9   | 12.0      | 6.4          | IgG        | k   |
| 10  | 8.2       | 10.5         | IgG        | k   |
| 11  | 7.0       | 4.8          | IgG        | k   |
| 12  | 7.8       | 3.2          | IgG        | k   |
| 13  | 141       | 7.8          | IgG        | k   |
| 14  | 5.5       | 3.4          | IgG        | k   |
| 15  | 6.5       | 3.4          | IgG        | k   |
| 16  | 7.5       | 3.4          | IgG        | k   |
| 17  | 8.0       | 3.4          | IgG        | k   |
| 18  | 8.5       | 3.4          | IgG        | k   |
| 19  | 9.0       | 3.4          | IgG        | k   |
| 20  | 9.5       | 3.4          | IgG        | k   |

UPN, unique patient number; Hb, hemoglobin; WBC, white blood cell; M protein, type; ISS, international staging system; NA, not available

| UPN | Hb (g/dL) | WBC (10^9/L) | M protein | ISS |
|-----|-----------|--------------|-----------|-----|
| 1   | 10.3      | 3.5          | IgG        | k   |
| 2   | 10.7      | 5.4          | IgG        | k   |
| 3   | 11.6      | 4.9          | IgG        | k   |
| 4   | 12.6      | 8.3          | IgG        | k   |
| 5   | 10.2      | 4.5          | IgG        | k   |
| 6   | 9.2       | 3.2          | IgG        | k   |
| 7   | 10.2      | 5.8          | IgG        | k   |
| 8   | 8.4       | 7.2          | IgG        | k   |
| 9   | 12.0      | 6.4          | IgG        | k   |
| 10  | 8.2       | 10.5         | IgG        | k   |
| 11  | 7.0       | 4.8          | IgG        | k   |
| 12  | 7.8       | 3.2          | IgG        | k   |
| 13  | 141       | 7.8          | IgG        | k   |
| 14  | 5.5       | 3.4          | IgG        | k   |
| 15  | 6.5       | 3.4          | IgG        | k   |
| 16  | 7.5       | 3.4          | IgG        | k   |
| 17  | 8.0       | 3.4          | IgG        | k   |
| 18  | 8.5       | 3.4          | IgG        | k   |
| 19  | 9.0       | 3.4          | IgG        | k   |
| 20  | 9.5       | 3.4          | IgG        | k   |

UPN, unique patient number; Hb, hemoglobin; WBC, white blood cell; M protein, type; ISS, international staging system; NA, not available

**Table 1.** Patient characteristics

| UPN | Age | Sex | M protein | ISS |
|-----|-----|-----|-----------|-----|
| 1   | 56  | M   | IgG       | 3   |
| 2   | 70  | M   | IgG       | 2   |
| 3   | 64  | M   | IgG       | 2   |
| 4   | 69  | M   | IgG       | NA  |
| 5   | 53  | F   | IgG       | 1   |
| 6   | 69  | F   | IgG       | 1   |
| 7   | 80  | F   | IgG       | 2   |
| 8   | 73  | M   | IgG       | 3   |
| 9   | 58  | F   | IgA       | 1   |
| 10  | 60  | F   | IgA       | 3   |
| 11  | 74  | F   | IgA       | 3   |
| 12  | 80  | F   | IgA       | 2   |
| 13  | 41  | M   | BIP       | 3   |
| 14  | 56  | M   | BIP       | 3   |
| 15  | 82  | M   | BIP       | 3   |
| 16  | 52  | F   | BIP       | 3   |
| 17  | 74  | F   | BIP       | 3   |
| 18  | 58  | M   | BIP       | 3   |
| 19  | 72  | F   | BIP       | 1   |
| 20  | 80  | F   | BIP       | 2   |
| 21  | 76  | F   | NS        | 3   |

UPN, unique patient number; ISS, international staging system; BIP, Bence Jones protein type; NS, non-secretory type; NA, not available

**Table 2.** Laboratory data

| UPN | Hb (g/dL) | WBC (10^9/L) | M protein | ISS |
|-----|-----------|--------------|-----------|-----|
| 1   | 10.3      | 3.5          | IgG        | k   |
| 2   | 10.7      | 5.4          | IgG        | k   |
| 3   | 11.6      | 4.9          | IgG        | k   |
| 4   | 12.6      | 8.3          | IgG        | k   |
| 5   | 10.2      | 4.5          | IgG        | k   |
| 6   | 9.2       | 3.2          | IgG        | k   |
| 7   | 10.2      | 5.8          | IgG        | k   |
| 8   | 8.4       | 7.2          | IgG        | k   |
| 9   | 12.0      | 6.4          | IgG        | k   |
| 10  | 8.2       | 10.5         | IgG        | k   |
| 11  | 7.0       | 4.8          | IgG        | k   |
| 12  | 7.8       | 3.2          | IgG        | k   |
| 13  | 141       | 7.8          | IgG        | k   |
| 14  | 5.5       | 3.4          | IgG        | k   |
| 15  | 6.5       | 3.4          | IgG        | k   |
| 16  | 7.5       | 3.4          | IgG        | k   |
| 17  | 8.0       | 3.4          | IgG        | k   |
| 18  | 8.5       | 3.4          | IgG        | k   |
| 19  | 9.0       | 3.4          | IgG        | k   |
| 20  | 9.5       | 3.4          | IgG        | k   |

UPN, unique patient number; Hb, hemoglobin; WBC, white blood cell; M protein, type; ISS, international staging system; NA, not available

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Table 3. Flow cytometry

| UPN | CD19 | CD20 | MPC1 | CD49e | CD56 | CD138 |
|-----|------|------|------|-------|------|-------|
| 1   | -    | -    | +    | -     | +    | -     |
| 2   | NA   | NA   | NA   | NA    | NA   | NA    |
| 3   | +    | -    | -    | -     | -    | -     |
| 4   | NA   | NA   | NA   | NA    | NA   | NA    |
| 5   | -    | NA   | -    | -     | -    | -     |
| 6   | -    | -    | +    | -     | -    | +     |
| 7   | -    | +    | +    | -     | +    | -     |
| 8   | -    | +    | +    | +     | +    | +     |
| 9   | -    | NA   | +    | +     | +    | -     |
| 10  | -    | NA   | +    | +     | -    | -     |
| 11  | -    | -    | -    | -     | +    | +     |
| 12  | -    | -    | -    | +     | +    | -     |
| 13  | NA   | NA   | NA   | NA    | NA   | NA    |
| 14  | -    | NA   | NA   | NA    | NA   | NA    |
| 15  | -    | -    | +    | -     | +    | -     |
| 16  | NA   | NA   | NA   | NA    | NA   | NA    |
| 17  | -    | +    | +    | -     | -    | +     |
| 18  | -    | -    | +    | -     | +    | -     |
| 19  | NA   | NA   | NA   | NA    | NA   | NA    |
| 20  | -    | -    | +    | -     | +    | +     |
| 21  | NA   | NA   | NA   | NA    | NA   | NA    |

UPN, unique patient number; NA, not available

Table 4. Immunohistochemistry

| UPN | CCND1 | CD38 | BCL2 | CD20 | PAX5 | BCL6 | SOX11 |
|-----|-------|------|------|------|------|------|-------|
| 1   | +     | +    | -    | -    | -    | -    | -     |
| 2   | +     | +    | -    | -    | -    | -    | -     |
| 3   | +     | +    | -    | -    | -    | -    | -     |
| 4   | +     | +    | -    | -    | -    | -    | -     |
| 5   | +     | +    | -    | -    | -    | -    | -     |
| 6   | +     | +    | -    | -    | -    | -    | -     |
| 7   | +     | +    | -    | -    | -    | -    | -     |
| 8   | +     | +    | -    | -    | -    | -    | -     |
| 9   | +     | +    | -    | -    | -    | -    | -     |
| 10  | +     | +    | -    | -    | -    | -    | -     |
| 11  | +     | +    | -    | -    | -    | -    | -     |
| 12  | NA    | NA   | NA   | NA   | NA   | NA   | NA    |
| 13  | NA    | NA   | NA   | NA   | NA   | NA   | NA    |
| 14  | +     | +    | -    | -    | -    | -    | -     |
| 15  | NA    | NA   | NA   | NA   | NA   | NA   | NA    |
| 16  | +     | +    | -    | -    | -    | -    | -     |
| 17  | +     | +    | -    | -    | -    | -    | -     |
| 18  | +     | +    | -    | -    | -    | -    | -     |
| 19  | +     | +    | -    | -    | -    | -    | -     |
| 20  | NA    | NA   | NA   | NA   | NA   | NA   | NA    |
| 21  | +     | +    | -    | -    | -    | -    | -     |

UPN, unique patient number; NA, not available

DISCUSSION

We evaluated 21 PCM patients with t(11;14)(q13;q32). The light chain-only (BJP type) was the most prevalent subtype (38%) in the current study, while a previous study has reported that the incidence of this subtype accounts for only 20% of all PCM patients.14 Robillard et al. reported a significantly high correlation between the expression of CD20 and t(11;14)(q13;q32) in PCM patients.5 However, Mateo et al. reported a lower incidence of CD20 expression in PCM with t(11;14)(q13;q32) (21 of 66 patients, 38%) in a larger study.6 We observed a lower incidence of CD20 expression (2 of 21 patients, 11%), which was in accordance with a report by Grigoriadis et al. (2 of 19 patients, 11%).7 Notably, the plasma cells of these patients exhibited lymphoplasmacytic cell morphology, which is a feature of PCM with t(11;14)(q13;q32).8

The down-regulation of PAX5 is essential for terminal differentiation into plasma cells,9 but the expression of PAX5 in PCM has also been previously reported in the literature.10,11 Torlakovic et al. reported focal or border-line expression of PAX5 in PCM, in which CD20 was also expressed.12 Lin et
Fig 2. May-Grünwald-Giemsa staining and immunohistochemistry. May-Grünwald-Giemsa staining (2a, UPN 7; 2d, UPN 17; 2g, UPN 3: original magnification ×1,000) and immunohistochemical analysis (2b-2c, UPN 7; 2e-2f, UPN 17; 2h-2i, UPN 3: original magnification ×400). May-Grünwald-Giemsa staining show the plasma cell myeloma cells in patients with t(11;14)(q13;q32) and CD20-positivity exhibit lymphoplasmacytic cell morphologies (2a, 2d). Immunohistochemical analysis show strong nuclear positivity of CCND1 (brown) (2b, 2c, 2h), and CD20 (brown) (2c, 2f). Two-color immunohistochemical analysis of PAX5 (blue) and CD138 (brown) show plasma cell myeloma cells expressing PAX5 (2i).
expressed in most PCM cells. In the current study, the expression but also t(9;14)(p13;q32). A complex variant translocation not only of t(11;14)(q13;q32) is a result of the translocation, because t(9;14;11)(p13;q32;q13) is an complex variant translocation not only of t(11;14)(q13;q32) but also t(9;14)(p13;q32).

BCL6 is a transcriptional repressor that is expressed in germinal center B-cells, and plays a crucial role in the formation of germinal centers. In the current study, the expression of BCL6 was not detected in PCM with t(11;14)(q13;q32). BCL2 is a protein that inhibits the apoptosis pathway, and is expressed in most PCM cells. CD56 is an adhesion molecule involved in cell-to-cell and cell-to-matrix interactions. Normal plasma cells lack CD56, whereas PCM cells express CD56 in 70-80% PCM patients. On the other hand, PCM with t(11;14)(q13;q32) is correlated with the lack of CD56 (82%). The expression of BCL2 was detected in all patients, and the expression of CD56 was observed in only 40% of patients in the current study.

The t(11;14)(q13;q32) translocation is commonly observed in PCM and mantle cell lymphoma (MCL). Abnormality of -13/13q is a common additional cytogenetic change in these diseases. In the current study, the frequency of -13/13q was 38%, which was in accordance with a report by An et al., they reported that the frequency of -13/13q in PCM with t(11;14)(q13;q32) (20 of 57 patients, 35%) was lower than that of PCM without t(11;14)(q13;q32) (99 of 191 patients, 52%). Furthermore, the allelic loss of 13q14-q34 was observed in 43-51% of MCL patients. The abnormality of del(17p) is also a common cytogenetic change in both PCM and MCL, the relevant gene of which is TP53, located on 17p13. The deletion of TP53 has been reported in 21-45% of MCL patients and 5-10% of PCM. We did not detect the deletion of TP53 in any of the four patients evaluated. The deletion of TP53 is infrequent in newly diagnosed PCM patients, and may be regarded as a later event in this disease.

SOX11 is a transcriptional factor expressed in the developing nervous system and plays a crucial role in neurogenesis, but is absent in many adult tissues. Recent studies showed that SOX11 is strongly expressed in the majority of MCL patients. In the current study, the expression of SOX11 was not detected in any PCM patients with t(11;14)(q13;q32). The t(11;14)(q13;q32) translocation is common in MCL and PCM with t(11;14)(q13;q32), but the expression of SOX11 is independent of this translocation and the resulting expression of CCND1, as mentioned by Dictor et al.

Although the number of patients was limited in the current study, the results suggest the absence of BCL6 and SOX11 expression, and infrequent expression of CD20, PAX5, and CD56 in PCM with t(11;14)(q13;q32), in contrast to the findings of earlier reports.

CONFLICT OF INTEREST: The authors declare no conflict of interest associated with this manuscript.

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