Hematological abnormalities in Jacobsen syndrome: cytopenia of varying severities and morphological abnormalities in peripheral blood and bone marrow

Jacobsen syndrome is caused by partial chromosomal deletion in the 11q23 region between sub-band 11q23.3 and telomeres, ranging from approximately 7 Mb to 20 Mb. Reportedly, various physical malformations and thrombocytopenia are considered common hematological comorbidities in Jacobsen syndrome, with 88.5% patients presenting with thrombocytopenia.[1,2] We retrospectively analyzed four patients who were diagnosed with Jacobsen syndrome in the Japanese cohort of 1,311 pediatric patients with bone marrow failure (BMF) and found thrombocytopenia alone in only one of the patients. The other three patients had multilineage cytopenias (pancytopenia in 1 and bicytopenia in 2). Careful evaluation of the literature revealed that, in nine of 31 patients, Jacobsen syndrome was complicated by multilineage cytopenias. These findings suggest that the hematological abnormalities of Jacobsen syndrome are not limited to the platelet system but may also involve multilineage blood cells.

Between February 2009 and December 2021, four patients (2 boys and 2 girls) in the Japanese BMF registry were diagnosed with Jacobsen syndrome, and they were enrolled in this study. Written informed consent was obtained from all the patients or their parents. The study was approved by the ethics committee of Nagoya University Graduate School of Medicine (2011–1352, 2019–0134). These patients had the following hematological abnormalities: thrombocytopenia (n=1), bicytopenia (thrombocytopenia + anemia, n=2), and pancytopenia (n=1). Their median age at cytopenia appearance was 60.5 months (range, 0-191 months) (Table 1). Although two patients required blood transfusion, none required hematopoietic stem cell transplantation. Other complications were listed in the *Online Supplementary Table S1*.

Case 1

A 10-year-old girl with pulmonary hypertension and ventricular septal defect (VSD) at birth was known to have Jacobsen syndrome diagnosed via chromosome analysis of 46,XX,del(11)(q23). A blood test performed during follow-up in the clinic revealed thrombocytopenia with a platelet count of 70×10^9/L, although her white and red blood cell counts were within normal range. Further, it was observed that her hemoglobin level decreased gradually and that she developed cytopenia in two lineages. She did not require transfusion and is currently being followed up without treatment.

Case 2

A girl was diagnosed with Jacobsen syndrome early after birth, but she had no prominent signs of cytopenia at the time of birth. A routine medical examination which she underwent at the age of 15 years revealed anemia and thrombocytopenia. Her chromosome test result was 46,XX,add(11)(q23.3). She had a white blood cell count of 3.1×10^9/L, a hemoglobin level of 8.4 g/dL, and a platelet count of 107×10^9/L. She did not require transfusion and is currently being followed up without treatment.

Case 3

A boy was born at 36 weeks of gestation with a low platelet count of 54×10^9/L, which further decreased gradually to 20×10^9/L. He also developed neutropenia (neutrophil count $=0.7\times10^9$/L) and anemia (hemoglobin level =8.4 g/dL). His chromosome test result was 46,XY,del(11)(q23.3). He had cardiac complications, such as VSD and aortic stenosis, for which he underwent surgery. Red blood cell and platelet transfusions were administered as needed during the perinatal period and before and after cardiac surgery. Currently, his blood cell counts are improving without treatment. He is under observation and does not require blood transfusion.

Case 4

A boy was born at 36 weeks and 5 days of gestation with a low platelet count of 46×10^9/L. He also had a complex congenital heart malformation (with VSD, hypoplastic left heart syndrome, mitral stenosis, truncus arteriosus, an interrupted aortic arch, and truncal valve regurgitation) and a horseshoe kidney. His chromosome test result was 46,XY,del(11)(q23.3). Currently, his platelet counts are improving without treatment; he is under observation and does not require blood transfusion.

Using mononuclear cell-derived DNA from peripheral blood samples, we performed whole genome sequencing (WGS) to identify pathogenic single-nucleotide variants and determine the extent of deletions in chromosome 11q. Genomic DNA was extracted from peripheral blood mononuclear cells using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). We detected germline variants using an established in-house pipeline.[3] In brief, we used a Burrows-Wheeler Aligner[4] to align to the hg19 reference genome. We evaluated the variants and WGS copy number

variations. Based on the variant interpretation guidelines of the American College of Medical Genetics, we functionally classified the identified variants into pathogenicity groups as follows: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.[5] Next, we used the Genomon 2.6.3 pipeline[6] and WGS data to evaluate structural variants (SV), including deletions, insertions, inversions, and translocations, in four patients diagnosed with Jacobsen syndrome. An SV analytic pipeline was used to identify deletions of 10.0–15.5 Mb between 11q23.3 and 11q25 in each of the four patients. The deletions were then validated using a comparative genomic hybridization array (SurePrint G3 Human CGH 2 × 400k Microarray [Agilent, Inc., Santa Clara, CA]) (Figure 1). However, we found no other pathogenic single-nucleotide variant that could affect the clinical phenotypes of the patients.

Table 1. Patient characteristics of our cohort and literature review.

Case	Deletion		Karyotype	Age in months	Sex	Cytopenia	Giant platelet	Reference
	Site	Size, Mb						
1	11q24.2–11q25	10.0	46,XX,del(11)(q23.3)	121	F	A, T	Y	This study
2	11q24.1–11q25	11.5	46,XX,add(11)(q23.3)	191	F	A, T	Y	This study
3	11q24.1–11q25	11.7	46,XY,del(11)(q23.3)	0	M	N, A, T	Y	This study
4	11q23.3–11q25	15.5	46,XY,del(11)(q23.3)	0	M	T	Y	This study
5	11q24.1–11q25	13.0	46,XY,del(11)(q23.3>qter)	0	M	T	Y	7
6	11q24.1–11q25	11.3	46,XX,del(11)(q23.3)	0	F	T	Y	S1
7	11q24.1–11q25	12.1	46,XX,del(11)(q24.1)	0	F	T	ND	S2
8	11q23.3–11q25	16.0	46,XX,del(11)(q23.3)	0	F	T	ND	S3
9	11q23.3–11q24	16.3	46,XX,del(11)(q23.3–qter)	ND*	F	T	ND	S4
10	11q24.1–11q25	12.5	ND	0	F	A, T	Y	10
11	11q24.1–11q25	11	ND	0	F	N, A, T	Y	10
12	11q24.2–11q25	9.3–9.5	ND	0	M	N, A, T	ND	S5
13	11q24.3–11q25	7.08	ND	0	M	N, A, T	ND	S6
14	11q23.3–11q25	ND	46,XY,del(11)(q23.3)	1	M	T	ND	S7
15	11q23.3–11q25	ND	46,XY,del(11)(q23.3)	0	M	T	ND	S8
16	11q23.3–11q25	ND	46,XY,del(11)(q23.3)	0	M	T	ND	S9
17	11q23.3–11q25	ND	46,XY,del(11)(q23.3)	0	M	T	ND	S9
18	ND	ND	46,XX,del(11)(q23.3)	6	F	N, A, T	ND	S10
19	ND	ND	46,XY,del(11)(q23.3)	60	M	T	ND	S10
20	ND	ND	46,XX,del(11)(q23)	72	F	T	ND	S10
21	ND	ND	46,XY,del(11)(q23)	20	M	T	ND	S10
22	ND	ND	46,XY,del(11)(q23)	18	M	T	ND	S10
23	ND	ND	46,XY,del(11)(q24.2)	29	M	N, A, T	ND	S10
24	ND	ND	46,XX,del(11)(q24.1)	18	F	N, A, T	ND	S10
25	ND	ND	46,XX,del(11)(q24.1)	65	F	N, A, T	ND	S10
26	ND	ND	46,XX,del(11)(q24.2)	180	F	T	ND	S10
27	ND	ND	46,XX,del(11)(q25)	45	F	T	ND	S10
28	ND	ND	46,XY,del(11)(q23.2)	6	M	N, A, T	Y	S11
29	ND	ND	46,XX,del(11)(qter)	0	F	T	ND	S12
30	ND	ND	ND	0	M	T	ND	S12
31	ND	ND	ND	0	F	T	ND	S13
32	ND	ND	ND	0	M	T	ND	S14
33	ND	ND	ND	0	M	T	ND	S15
34	ND	ND	ND	0	F	T	ND	S16
35	ND	ND	ND	0	F	T	ND	S17

*Pubertal age. ND: not determined; F: female; M: male; N: neutropenia; A: anemia; T: thrombocytopenia; Y: yes; S1–S17: Supplementary References (*Online Supplementary Table S2*).

Aside from giant platelets, few studies have evaluated the morphological features of the cells of Jacobsen syndrome patients.[7] Smear samples were taken from the peripheral blood and bone marrow of the Jacobsen syndrome patients in our cohort. These were evaluated by physicians (AH, MI, and HI) with expertise in pediatric hematological morphology. Peripheral blood morphology could be evaluated for all four patients, whereas bone marrow morphology could be evaluated only for the three patients with pancytopenia or bicytopenia. Consistent with the findings of a previous study,[2] we observed giant platelets in the peripheral blood. We also found abnormal neutrophil segmentation in the peripheral blood and dysmorphic megakaryocytes in the bone marrow. These may be common hematological phenotypes in patients with Jacobsen syndrome (Figure 2). However, as these features have not been previously reported, future verification with larger patient samples is required.

We conducted a literature search on August 31, 2022. The PubMed database (https://pubmed.ncbi.nlm.nih.gov) was searched for articles published between 1977 and August 2022. The search terms included Jacobsen syndrome, thrombocytopenia, anemia, neutropenia, and pancytopenia. The literature search extracted 14 articles written in English, and a manual literature search identified five additional relevant articles. Thus, a total of 19 articles were found to be eligible for literature review. After careful examination of the abstracts and main texts of the ar-

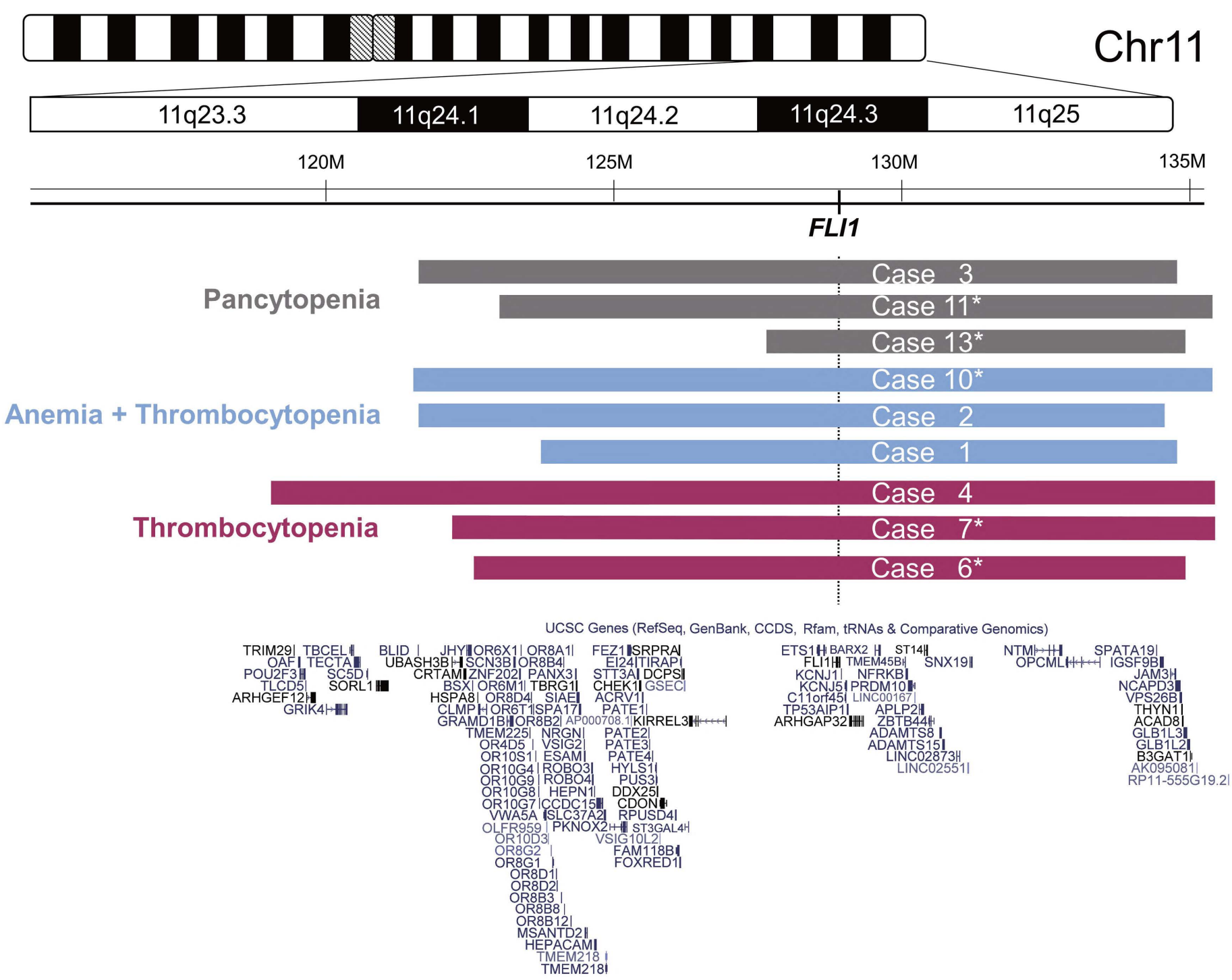

Figure 1. Scheme of chromosomal deletions of 11q23.3-qter in Jacobsen syndrome. Black lines indicate patients with pancytopenia, blue lines indicate patients with anemia and thrombocytopenia, and red lines indicate patients with thrombocytopenia. The deletion regions were identified via whole genome sequencing (WGS) in the 4 patients in our cohort (cases 1–4) and via comparative genomic hybridization array (*) in 5 patients from our literature review (cases 6, 7, 10, 11, and 13). Genes within chromosomal deletion regions are shown on a screenshot of the UCSC genome browser (http://genome.ucsc.edu; accessed on May 4, 2023). Chr: chromosome; tRNA: transfer RNA.

ticles, we identified 31 Jacobsen syndrome patients with hematological abnormalities. These were thrombocytopenia (n=22), pancytopenia (n=8), and bicytopenia (n=1) (Table 1; *Online Supplementary Figure S1*). The median age of cytopenia onset was 0 months (range, 0–191 months) in all 35 patients, including four patients in our cohort (Table 1; *Online Supplementary Table S2*). Of the 31 patients with Jacobsen syndrome who showed hematological abnormalities, two patients also showed immunological abnormalities (low IgG in 1 and low IgM in the other). Data were available on the gestational week of 12 of the 31 patients. Of these 12, four were born prematurely; three with thrombocytopenia alone, and one with pancytopenia.

Patients with Jacobsen syndrome are at risk of multilineage cytopenias and should be followed up closely, with attention to bleeding symptoms and infections. During the follow-up period, it is important to consider red blood cell and platelet transfusions before even minor surgical interventions. Patients should be instructed to strictly adhere to the vaccination schedule.

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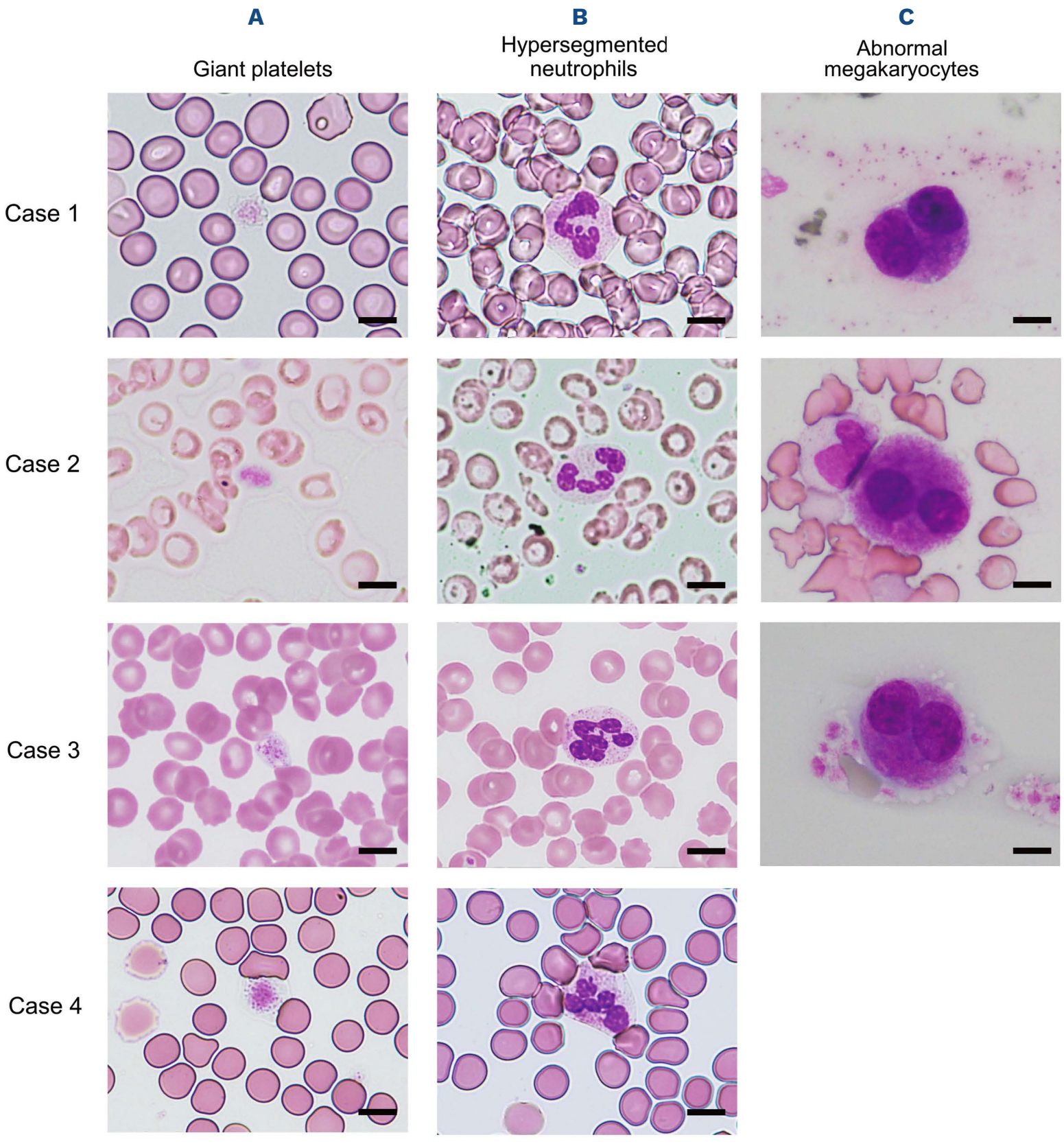

Figure 2. Morphological abnormalities in peripheral blood and bone marrow. May-Giemsa staining of peripheral blood and bone marrow smears. The black bar represents the scale and is equivalent to 10 μm. (A) Giant platelets in the peripheral blood of all 4 patients (case 1-4). (B) Hypersegmented neutrophils in peripheral blood. (C) Abnormal morphology of bone marrow megakaryocytes.

integration 1 transcription factor (*FLI1*) plays a crucial role in the thrombocytopenia observed in Jacobsen syndrome.[8] *FLI1* was included in the extent of deletion of the long arm of chromosome 11 observed in all four newly diagnosed patients with Jacobsen syndrome in our cohort, and this finding is consistent with the results of previous studies.[8–9] After combining the five patients with a clear extent of deletion who were identified in the literature review with the four patients in our cohort to obtain a total of nine patients, we evaluated the association between chromosome deletion site and severity of cytopenia in the nine patients; we did not find a clear association between deletion size or deletion of a specific gene and the severity of cytopenia (Figure 1). Although *FLI1* may be involved in anemia and/or neutropenia as well as thrombocytopenia, we believe that the accumulation of future cases might reveal regions of deletion associated with the severity of hematological phenotypes.

The current study has some limitations. We included a small number of patients, and the observation period was limited to childhood. Further, we observed fluctuations in the severity of cytopenia in some patients in our cohort. Future larger longitudinal studies must clarify the clinical picture of multilineage cytopenia and its molecular pathogenesis in patients with Jacobsen syndrome. Preterm delivery and other pregnancy-related risk factors induce epigenetic changes including DNA methylation.[10] This can influence the degree of cytopenia observed in patients with Jacobsen syndrome. However, information on the gestational week was only available for a subset of cases in our cohort. Therefore, further investigation is warranted.

In conclusion, multilineage cytopenia might be a recurrent finding in Jacobsen syndrome, and giant platelets, abnormal segmentation of neutrophils, and dysmorphic megakaryocytes may be considered blood cell morphological abnormalities associated with this syndrome.

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Disclosures

No conflicts of interest to disclose.

Contributions

DY, HM, AN, MW, and Y Tsumura performed laboratory work, gathered clinical information, designed and conducted the study, analyzed data, and wrote the paper. AH, M Ito, HI, and YO performed laboratory work, gathered clinical information, and analyzed data. SK and Y Takahashi directed the study and analyzed the data. NN, RT, SK, KN, M Imaya, AY, RM, and DS performed laboratory work and gathered clinical information. NF, KK, KU, and EM gathered clinical information. All authors reviewed and approved the final version of the manuscript.

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Data-sharing statement

The data used in this study will be provided to qualified researchers on reasonable request.

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