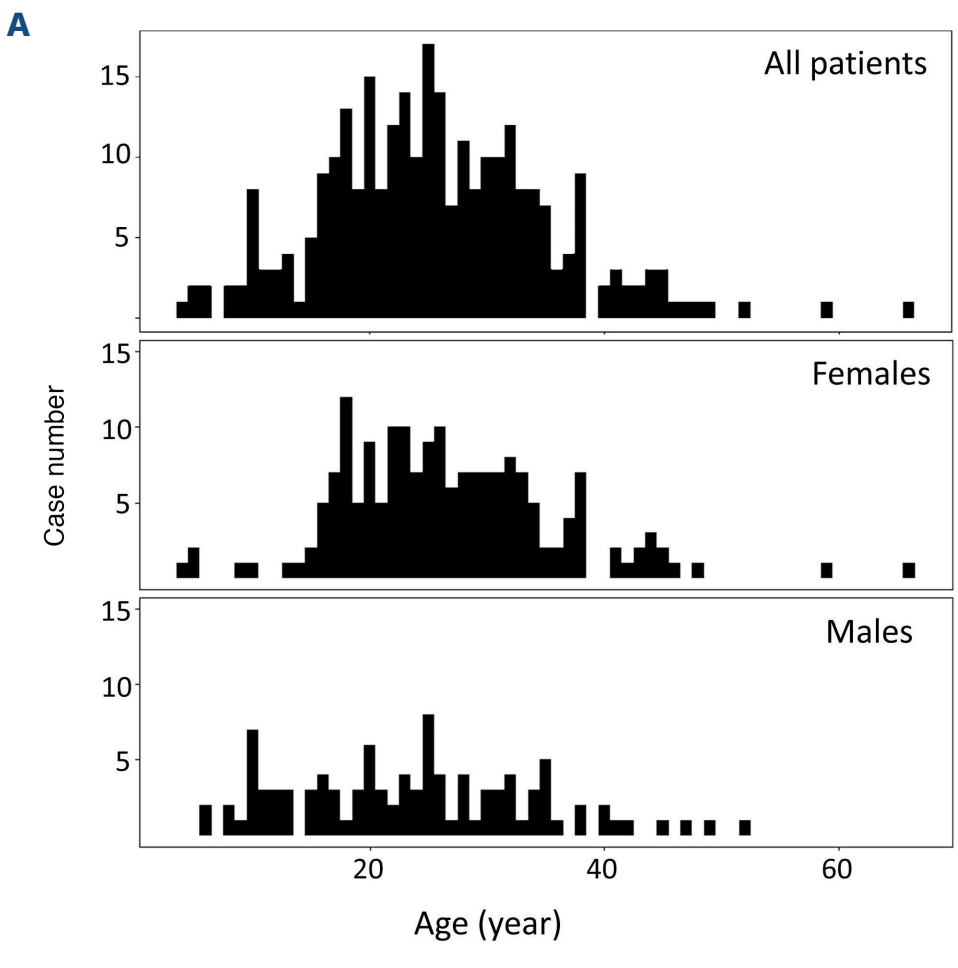
Blood cell and marrow changes in patients with Kikuchi disease

Kikuchi disease (KD) is a self-limiting lymphadenitis,[1,2] common in East Asia[3] but rare in other countries.[1] Although it most often affects young adults, it can occur at any age.[1,2] Abnormal blood cell counts are the most well-known laboratory abnormality.[1,2] In this study, we reviewed blood cell counts and bone marrow studies in patients with KD. We found that the rates and recovery time of abnormal cell counts differ between age groups; children more commonly develop pancytopenia, and their anemia frequently persists for several months. Bone marrow and reticulocyte data suggest that myelosuppression is the mechanism responsible for cytopenia. Few patients with KD developed hemophagocytic lymphohistiocytosis (HLH). The blood and marrow changes were distinctly different between KD and HLH.

We screened 367 patients with KD, and 282 (77%) had complete blood count (CBC) data: 101 were male, and 181 were female (M:F=0.56). The mean age was 26±10 (range, 4–66) years. On average, female patients were older than male patients (27± 9 *vs*. 24±10 years, *P*=0.009). Female patients predominantly developed KD in young adulthood, but the age distribution for male patients was relatively even (Figure 1A). Children younger than 15 years with KD were predominantly male (M:F=2.67), and patients older than 15 were predominantly female (Figure 1B). Few researchers have pointed out the sex ratio difference between children and adults. However, all previous adult-including studies identified female patients as predominant, with a male–female ratio ranging from 0.28 to 0.91.[4-6] By contrast, most pediatric studies have reported male patients as predominant or a male–female ratio close to one.[7,8] Many experts consider the predominance of female patients with KD controversial.[1,2] We believe the difference is related to the age of patients.

The frequency of abnormalities is presented in Figure 1C. The definitions of abnormalities are listed in the *Online Supplementary Table S1*. Of the 282 patients, anemia (22%) was the most common abnormality, followed by lymphopenia (17%), neutropenia (11%), atypical lymphocytes (9%), and thrombocytopenia (8%). Increased cell counts were relatively rare. The results were similar to previous reports.[5,9-11] We also found that most cytopenias occurred in a single cell lineage. Pancytopenia (2%) and bicytopenia (5%) were uncommon.



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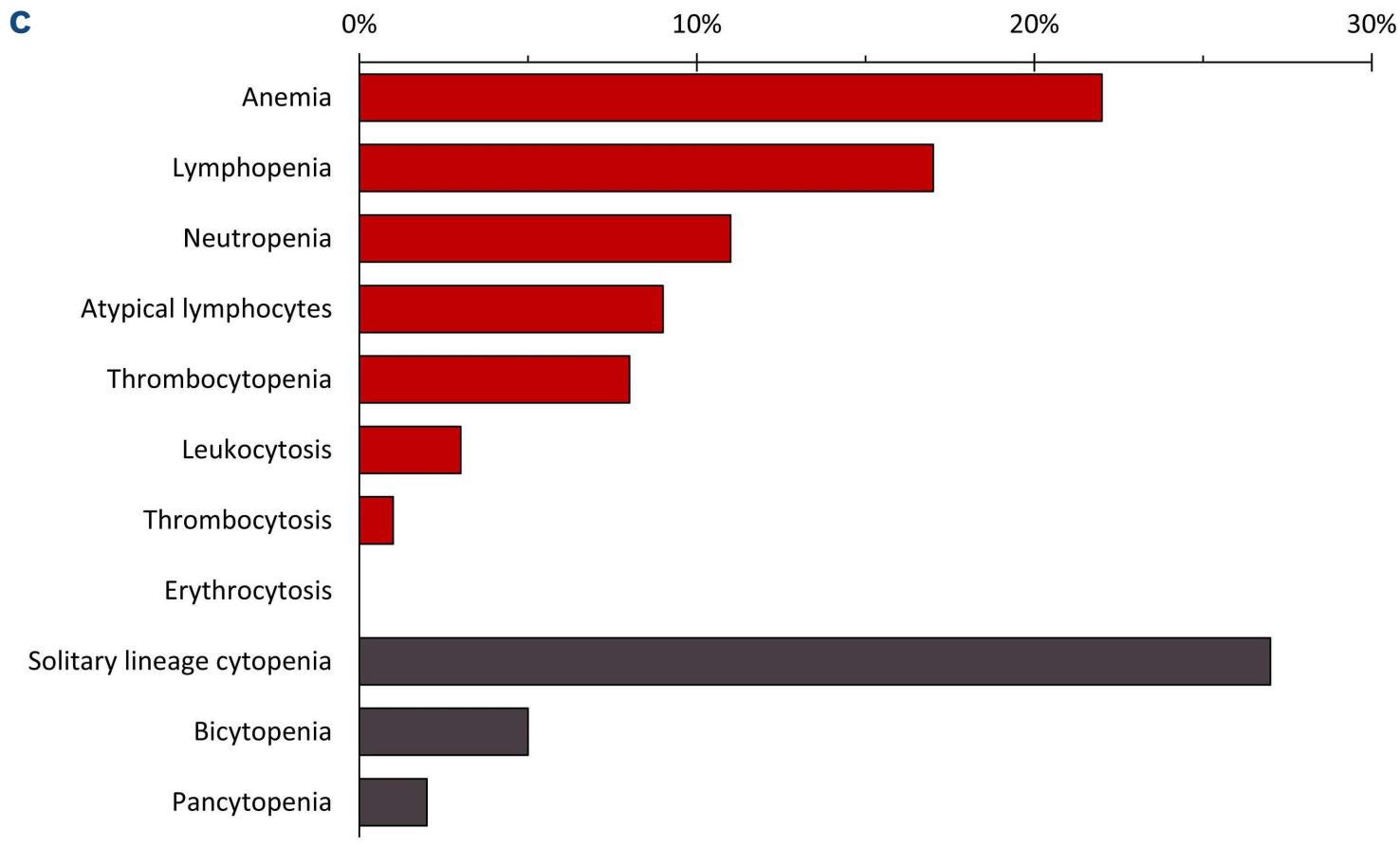

Figure 1. Frequency of abnormal blood cell counts. (A) Age distribution of all patients (upper), female patients (middle), and male patients (lower). (B) Percentage of male (black) and female (gray) patients by age group. (C) Frequency of abnormal cell counts.

We plotted the frequency of abnormal cell counts by age group, revealing that the abnormalities exhibited a similar bimodal distribution (Figure 2A). Young adults had the lowest rate, and children and middle-aged patients had higher abnormality rates. The rate of lymphopenia was significantly different between age groups (P<0.001). For all the abnormalities, pairwise comparisons revealed significant differences between age groups (Figure 2A).

Likewise, the distribution of pancytopenia and bicytopenia also exhibited bimodal patterns (Figure 2B). The rates of pancytopenia differed between age groups (P=0.024). Children younger than 15 years had a higher rate of pancytopenia than patients in other age groups (adjusted P=0.008). The results suggest that patients of extreme ages, especially children, are more vulnerable to cytopenia.

We reviewed the follow-up CBC in these patients. The recovery time, summarized in Figure 2C, varied considerably, ranging from days to months. Cytopenia can persist for months in patients with KD—considerably longer than lymphadenopathy, which resolves within weeks.[1,2] Anemia (34%) was the cytopenia that most frequently persisted for more than 6 months, and lymphopenia (4%) was the least likely to persist that long.

Like the abnormality rates, the late recovery rates varied by age. We plotted the case numbers by age group (Figure 2D). Anemia usually lasted more than 6 months in children, occasionally did so in middle-aged patients, but never lasted in young adults (P<0.001). Likewise, thrombocytopenia, neutropenia, and lymphopenia lasted more than 6 months in some patients of extreme ages but were absent in 16–25-year-old patients (Figure 2D).

In summary, children more frequently develop cytopenias, and their cytopenias are more protracted than those of young adults. Therefore, pediatricians should be aware of cytopenias in children with KD.

We further explored the mechanism underlying the abnormal blood cell counts. First, all the available reticulocyte count data (n=8) indicated a low erythropoietic response to anemia. Second, we reviewed bone marrow studies. Sixteen (6%) patients had undergone bone marrow biopsy (Table 1) and 88% (14/16) had hypocellular marrow with little compensatory hematopoiesis. A previous study has demonstrated that the serum of patients with KD suppressed granulopoiesis *in vitro*.[2] Our clinical observation is consistent with their results.

We quantified CD68+ histiocytes and CD123+ plasmacytoid dendritic cells in the bone marrow biopsy. Compared with that of age-matched controls, the bone marrow in patients with KD did not display increased histiocytes or plasmacytoid dendritic cells (*Online Supplementary Figure S1*). In most patients with KD, the lymphadenopathy features should be absent from bone marrow.

Two of the patients in our study developed HLH (cases 5 and 10 in Table 1). The prevalence of HLH was 0.71% (2/282) in patients with CBC data and 0.54% (2/367) in all the patients screened. The prevalence of HLH was 0–3% in the literature.[4,5,11,12]

HLH is the most frequently reported bone marrow finding

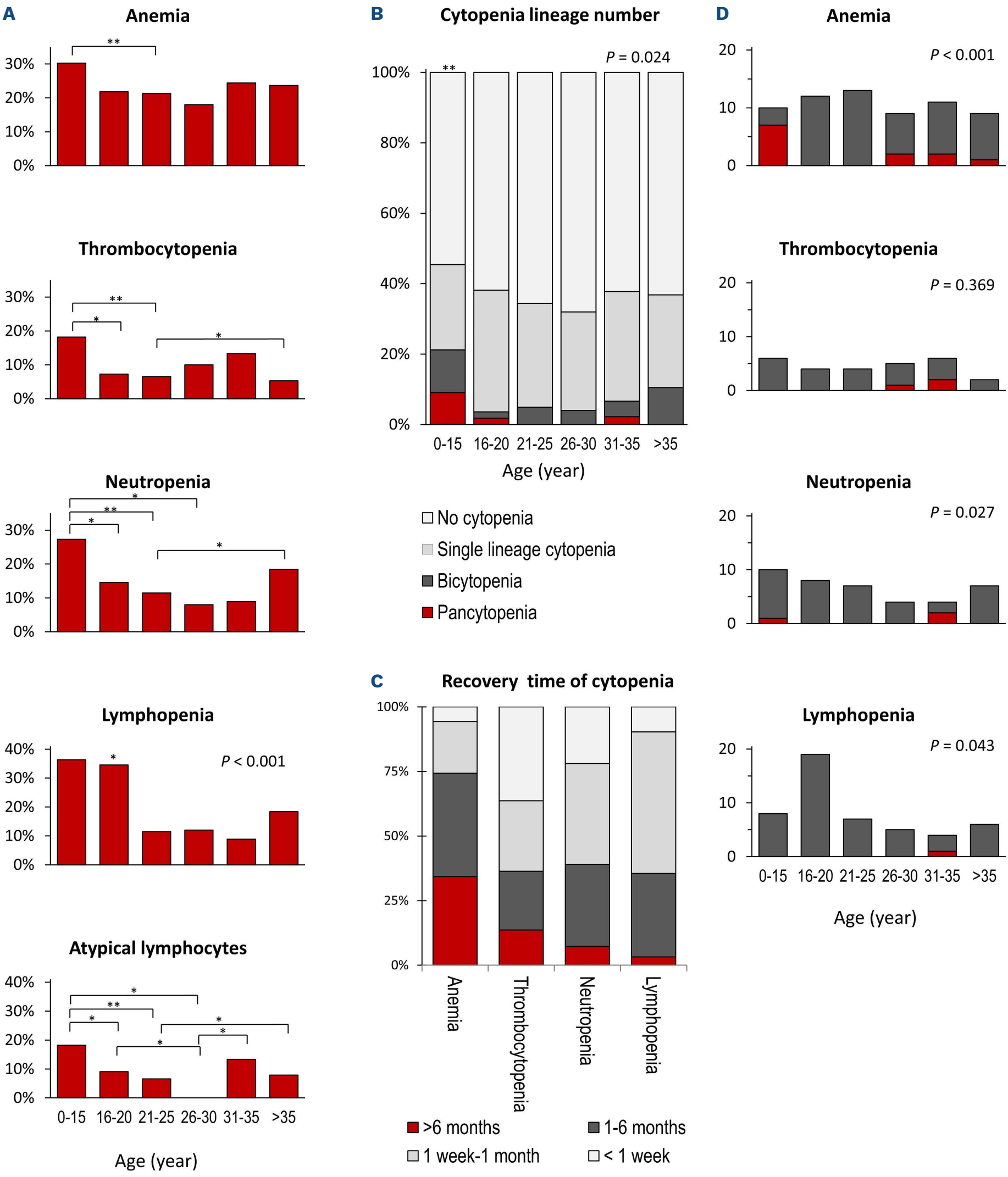

Figure 2. Abnormal rates by age group and cytopenia recovery. (A) Frequency of abnormal blood cell counts by age group. (B) Cytopenia lineage number by age group. The adjusted *P*-value of the *post hoc* test and pairwise comparison are denoted by *$P<0.05$; **$P<0.01$. (C) Recovery time by type of cytopenia. (D) Case number of patients with and without late recovery (red and gray bars, respectively) by age group.

in patients with KD,[13] but most patients with KD do not have HLH. We compared our cases with an independent cohort of patients with HLH to investigate the differences between HLH and KD. The HLH cohort included 133 patients: 80 were males and 53 were females, with a higher percentage of males than KD (*P*<0.001). The mean age was 50 (range, 2–91) years, older than KD (*P*<0.001). This HLH cohort has been partially published in a previous study.[14]

The patients with KD (n=282) had higher hemoglobin levels (13.0±1.6 *vs*. 8.5±1.4 g/dL, *P*<0.001) and higher platelet counts (240±76 *vs*. 67±84 × 10^3/μL, *P*<0.001) than those with HLH (n=133; *Online Supplementary Figure S2*). The patients with KD had lower rates of anemia (23% *vs*. 98%, *P*<0.001), thrombocytopenia (10% *vs*. 92%, *P*<0.001), and neutropenia (14% *vs*. 38%, *P*<0.001) than did the patients with HLH (*Online Supplementary Figure S2*). With regard to severity, patients with KD had lower rates of severe anemia (8% *vs*. 69%, *P*<0.001), thrombocytopenia (19% *vs*. 96%, *P*<0.001), and neutropenia (33% *vs*. 80%, *P*<0.001; *Online Supplementary Figure S2*). In terms of the number of cytopenia lineages, only 1% (4/282) of patients with KD had more than two lineages of severe cytopenia in contrast to 72% (96/133) of patients with HLH (*P*<0.001). Moreover, patients with KD (n=16) had lower bone marrow cellularity (34±25% *vs*. 63±21%, *P*<0.001) and less histiocytic infiltrate (10± 7% *vs*. 29±28%, *P*<0.001) than those with HLH (n=133; *Online Supplementary Figure S2*).

Cytopenias are present in both patients with KD and HLH, but the frequency and severity are much lower in those with KD. HLH typically exhibits increased cellularity, histiocyte infiltrates, and hemophagocytosis in bone marrow.[14,15] By contrast, KD exhibits decreased cellularity and no increase in histiocytes.

In summary, we report comprehensive blood changes in patients with KD. Patients of extreme ages are more susceptible to cytopenias, which can persist for several months. The mechanism underlying cytopenias is probably mild myelosuppression. Patients with HLH exhibit severe cytopenias and compensatory hematopoiesis, but those with KD exhibit mild cytopenia and hypocellular marrow.

Table 1. Patients with bone marrow studies.

			Peripheral blood								Bone marrow biopsy				Bone marrow aspirate smear				
No	**Age yr**	**Sex**	**WBC x10⁹/L**		**HB g/dL**		**PLT x10⁹/L**		**ANC x10⁹/L**		**Cell**	**Mye**	**Ery**	**MK**	**Cell**	**Mye**	**Ery**	**MK**	**HPh**
1	4	F	3.32	↓	9.6	↓	250		2.00		↓	N	N	N	↓	↓	↓	↓	(–)
2	8	M	2.32	↓	11.7		136	↓	0.68	↓ ↓	↓ ↓	N	N	N	N	N	N	N	(–)
3	9	M	3.33	↓	11.0	↓	160		1.50		↓ ↓	N	N	N	↓ ↓	N	N	N	(–)
4	11	M	2.23	↓	8.9	↓ ↓	84	↓ ↓	1.33	↓	↓	N	N	↑	N	N	N	↑	(–)
5	16	M	2.47	↓	13.7		179		2.10		↓ ↓	N	↓	N	↓ ↓	↓	↓ ↓	N	(+)
6	17	F	4.89		13.1		273		1.55		↓ ↓	N	N	N	↓ ↓	↓	↓ ↓	↓ ↓	(–)
7	18	F	1.64	↓	12.2		92	↓ ↓	0.62	↓ ↓	↓ ↓ ↓	N	N	N	↓ ↓	↓	↓ ↓	↓ ↓	(–)
8	19	F	3.40	↓	11.1	↓	344		2.67		↓ ↓	N	↓	N	↓ ↓	↓ ↓	↓ ↓	↓ ↓	(–)
9	26	M	1.22	↓	15.1		90	↓ ↓	0.43	↓ ↓	↓ ↓ ↓	N	N	N	↓ ↓ ↓	↓ ↓ ↓	↓ ↓ ↓	N	(–)
10	28	M	1.83	↓	14.5		87	↓ ↓	1.37	↓	↓ ↓ ↓	N	N	N	N	N	N	N	(–)
11	31	M	2.22	↓	11.5	↓	241		1.25	↓	↓ ↓ ↓	N	N	N	N	N	N	N	(–)
12	36	M	2.80	↓	13.5		265		1.83		↓	N	N	N	N	N	N	N	(–)
13	36	F	2.39	↓	12.2		255		1.15	↓	↓ ↓	N	N	N	↑	↑	↑	↑	(–)
14	38	F	1.89	↓	8.2	↓ ↓	211		1.13	↓	↑ ↑	↑	N	N	↑	↑	N	↑	(–)
15	41	F	2.81	↓	10.6	↓	221		1.85		↓ ↓	N	N	N	↓ ↓	↓	↓ ↓	↓ ↓	(–)
16	66	F	19.89		10.4	↓	398		18.14		↑ ↑	↑	N	↑	↑	↑	↓	N	(–)

ANC: absolute neutrophil count; Cell: cellularity; Ery: erythroid; F: female; HB: hemoglobin; HPh: hemophagocytosis; M: male; MK: megakaryocyte; Mye: myeloid; N: no specific change; No: number; PLT: platelet; WBC: white blood cell; yr: year.

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Contributions

S-CY designed the study, reviewed bone marrow trephine biopsies, and drafted the manuscript; H-HH reviewed the laboratory data and bone marrow aspirate smears and critically revised the manuscript; C-NC, T-CC, T-LY collected clinical data.

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Data-sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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