Long-term survival with RAS-associated autoimmune leukoproliferative disorder with somatic KRAS mutation: A case report

Hideto TERANISHI, Shoko WAKABAYASHI, Mina KONO, Sahoko ONO, Atsushi KATO, Eisuke KONDO, Hiroto AKAIKE, Ippei MIYATA, Satoko OGITA, Naoki OHNO, Tomohiro OISHI, Mitsuo MASUNO, Kazunobu OUCHI

Department of Pediatrics, Kawasaki Medical School

ABSTRACT  RAS-associated autoimmune leukoproliferative disorder (RALD) is a recently reported rare nonmalignant autoimmune disorder. The characteristic clinical findings of RALD include monocytosis, leukocytosis, lymphoproliferation, and autoimmune phenomena. RALD is defined by somatic mutations in KRAS or NRAS. It is a new disease that was reported by Niemela and Takagi in 2011. The prognosis and incidence are currently unknown and the treatment strategy has not yet been established.

Here we describe the long-term survival of a patient with who displayed a somatic KRAS G12D mutation. His clinical features and labolatory data were overlapped with juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. Mercaptopurine hydrate, hydroxycarbamide and azacitizine were administered to control white blood cell count and improve clinical symptoms. He had a long survival time without hematopoietic stem cell transplantation.

doi: 10.11482/KMJ-E201945009  (Accepted on May 11, 2019)

Key words: RAS-associated autoimmune leukoproliferative disorder, azacitizine

INTRODUCTION  RAS-associated autoimmune leukoproliferative disorder (RALD) is a chronic, non-malignant condition that characterized by monocytosis, leukocytosis, lymphoproliferation, and autoimmune phenomena. RALD is a new class of monogenic autoimmune diseases.

Patients with RALD show overlap of clinical features and laboratory data with patients with juvenile myelomonocytic leukemia (JMML), chronic myelomonocytic leukemia (CMML), and autoimmune lymphoproliferative syndrome (ALPS).

RALD is caused by activation of RAS-family proteins, including NRAS and KRAS. KRAS is a gene that acts as an on/off switch for cell signaling. When it functions normally, it controls cell proliferation. When it is mutated, negative signaling is disrupted. Therefore, cells can continuously proliferate and often develop into cancers. The prognosis of RALD is unknown because there are very few cases.

We observed the long-term survival of a patient...
with RALD who displayed a somatic \textit{KRAS} G12D mutation.

\textbf{CASE REPORT}

A 6 month-old boy presented with bilateral cervical lymphoadenopathy, splenomegaly, and moderate anemia. Bone marrow (BM) aspiration and a trephine biopsy were performed. His BM revealed normocellular marrow with evident erythrodysplasia and 2\% blasts involving trisomy 8. The patient was diagnosed with myelodysplastic syndrome (MDS). His parent refused hematopoietic stem cell transplantation (HSCT), and he remained under observation with red blood cell concentrate transfusion. At the age of 13 years, he had a remarkably short stature of -5.3 SD and a low weight of -3.0 SD (Fig. 1).

He had taken mercaptopurine hydrate to control his splenomegaly since the age of 6 years, but his splenomegaly gradually worsened, and put pressure on his gastrointestinal tract. By the age of 13 years, he was unable to consume food because of the

![Fig. 1. Physical examination at the age of 18 years](image)

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Blood chemistry</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 34,540 / (\mu l)</td>
<td>TP 8.2 g/dl</td>
<td>NCC 28.2 (\times 10^9 / \mu l)</td>
</tr>
<tr>
<td>Neut 73 %</td>
<td>Alb 2.4 g/dl</td>
<td>Megk 69.4 / (\mu l)</td>
</tr>
<tr>
<td>Lym 2 %</td>
<td>T.Bil 1.3 mg/dl</td>
<td>Blast 0.2 %</td>
</tr>
<tr>
<td>Mon 25 %</td>
<td>AST 30 U/l</td>
<td>Eo 0.6 %</td>
</tr>
<tr>
<td>Eos 0 %</td>
<td>ALT 17 U/l</td>
<td>Baso 0.2 %</td>
</tr>
<tr>
<td>Baso 0 %</td>
<td>LDH 470 U/l</td>
<td>Myeloid series 47.4 %</td>
</tr>
<tr>
<td>RBC 264 (\times 10^6 / \mu l)</td>
<td>ALP 1116 U/l</td>
<td>Mono 22.2 %</td>
</tr>
<tr>
<td>Hb 9.0 g/dl</td>
<td>(\gamma)-GTP 333 U/l</td>
<td>Erythroid series 15.8</td>
</tr>
<tr>
<td>HbF 1.0 g/dl</td>
<td>BUN 17 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Ht 27.6 %</td>
<td>Cr 0.21 mg/dl</td>
<td></td>
</tr>
<tr>
<td>MCV 104.5 fl</td>
<td>UA 4.7 mg/dl</td>
<td></td>
</tr>
<tr>
<td>MCH 34.1 pg</td>
<td>Glu 96 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Plt 24.7 (\times 10^9 / \mu l)</td>
<td>CRP 6.41 mg/dl</td>
<td>Spontaneous colony (-)</td>
</tr>
<tr>
<td>PT 9.3 sec</td>
<td>Na 128 mEq/l</td>
<td>GM-CSF hypersensitivity (-)</td>
</tr>
<tr>
<td>APTT 33.0 sec</td>
<td>K 2.9 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen 520 mg/dl</td>
<td>Cl 90 mEq/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ca 7.8 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P 3.2 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgG 2,780 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgA 1,398.3 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgM 481.1 mg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ANA 28.3 (+)</td>
<td></td>
</tr>
</tbody>
</table>
splenomegaly. He underwent a splenectomy, and
the pressure on the intestinal tract was reduced.
However, a hematological examination showed a
white blood cell (WBC) count of 31,300 - 121,800/µL
with monocytosis (2,308 - 29,841/µL).

His serum levels of immunoglobulin (Ig) G,
IgA, and IgM were 2,780, 1,398 and 481 mg/dL,
respectively. His antinuclear antibodies were mildly
positive, and his HbF did not increase (Table 1).

He presented with fever, rash, and arthralgia
because of the WBC count increase; hydroxycarbamide
was used to control his WBC count. Rashes
appeared as small red bumps on his arms, legs,
neck, and trunk were associated with pain; therefore
we diagnosed Sweet’s syndrome. Treatment with
a corticosteroid was effective, but the rashes
recurred frequently. He also had deafness in his
right ear at the age of 14 years, and his hearing
loss was irreversible (Fig. 2). A peripheral blood
smear evaluation showed absolute monocytosis
with 1% circulating blast. An assessment of his
BM revealed severe hyperplasia, monocytosis, and
dysplasia with megaloids, micromegakaryocytes,
ringed neutrophils, and hypersegmented neutrophils
(Fig. 3). However, BM contained only 1% blasts
involving trisomy 8. The Spontaneous colony
and GM-CSF hypersensitivity assessments
were negative. Therefore, we diagnosed CMML
transformed from MDS.

To reduce leukocytosis and improve clinical
symptoms, he was administered six cycles of
azacitizine (AZA) (75 mg/m2, day1-5, each
cycle every 4 weeks) at the age of 17 years. The
percentage of bone marrow blasts did not change
from 1% to 2% before and after AZA. All cell
line did not reach normal maturation. Complete
remission was not achieved, but his clinical data and
symptoms improved. The white blood cell count
decreased and hepatomegaly was reduced. The fever
was relieved and the rash with pain disappeared
(Fig. 2). Following this, a somatic KRAS c.35 G>A
mutation was found, and he was diagnosed with
RALD (Fig. 4). Other JMML and ALPS related gene mutations were not detected.

The patient died due to liver failure at the age of 19 years.

DISCUSSION

RALD is a rare disease caused by a RAS pathway mutation. It is characterized by lymphoproliferation with an increase of CD4-CD8- double negative T cells. The clinical features includes monocytosis, leukocytosis, splenomegaly, and hypergammaglobulinemia. Furthermore, in some patients, this disease occurs in combination with autoimmune diseases such as systemic lupus erythematosus, Rosai-Dorfman syndrome, and Sweet’s syndrome. In some patients, an increase in HbF and GM-CSF hypersensitivity has been confirmed. RALD is caused by the activation of RAS-family proteins, including NRAS and KRAS. RALD is considered a disease that shares some
clinical features and molecular genetic abnormalities with other leukoproliferative diseases, such as ALPS, JMML, and CMML (Fig. 5). Several cases have been reported, but the prognosis and standard treatment remain unclear. RALD is a slow disease, but some cases have been reported with rapid progression and pulmonary infiltration\(^\text{3–5}\).

Allogenic HSCT is the only treatment for patients with RALD. However, one opinion recommends avoiding aggressive interventions, such as HSCT, in patients with RALD without clear evidence of malignancy\(^5\). Toyoda et al reported that rituximab could improve the clinical response and quality of life of patients with RALD\(^8\).

For our patient, we administered mercaptopurine hydrate, hydroxycarbamide, and AZA for improving the clinical symptoms and suppressing the WBC count before RALD was diagnosed.

Hypomethylating drugs are useful for the management of MDS and CMML\(^9,10\). Costa et al reported an overall response rate of 39% (14 of 36) when AZA was administered to patients with CMML\(^9\). The disorder did not reach remission with AZA treatment, but the condition remained stable, and some improvements in clinical symptoms were observed. Accumulation of the use experience for children is expected in the future.

Our report has several limitations. We did not estimate the TCR\(\alpha\beta+\text{CD}4-\text{CD}8^-\) double negative T cell and conduct an apoptosis assay. Therefore, differentiation from other autoimmune diseases such as ALPS and JMML, may be difficult.

Transformation from MDS to CMML is rarely observed. After being diagnosed with MDS at the age of 6 months based on BM examination, the patient did not undergo a splenectomy until the age of 13 years because his parents did not want invasive treatment. Therefore, the evaluation of disease activity may have been insufficient.

In summary, we report the long-term survival of a patient with RALD with a somatic KRAS mutation. The pathological condition and prognosis of RALD
have not yet been elucidated, and further study of cases is necessary.

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

REFERENCES