**Abstract:**
Patients with near tetraploidy/tetraploidy (NT/T)-acute myeloid leukemia (AML) are rare and generally show poor survival. A 62-year-old man was referred to our hospital with pancytopenia. A bone marrow examination revealed the proliferation of extremely large blasts, and led to the diagnosis of AML M0. A cytogenetic analysis showed an NT-karyotype of 91, XXYY, -5, add(18)(p21),del(20)(q12q13)×2. Complete remission was achieved with single remission induction chemotherapy. Although consolidation chemotherapies were not available because of his critical condition, he remained in remission and survived for more than 40 months without cytopenia. However, repeated bone marrow examinations showed persistent clonal hematopoiesis with del(20)(q12q13) without apparent myelodysplasia.

**Key words:** near tetraploidy, acute myeloid leukemia

**Introduction**
Tetraploidy (4n, 92 chromosomes) and near-tetraploidy are rare cytogenetic alterations in acute myeloid leukemia (AML) (1). Near-tetraploidy/tetraploidy (NT/T)-AML has been reported to occur preferentially in elderly male patients and is morphologically characterized by very large blasts (2, 3). Some cases have been reported to be associated with extensive erythrophagocytosis by leukemic blasts (4-6). Cases of NT/T-AML generally show a dismal prognosis, and the median overall survival (OS) is reported to be 5-9 months (1-3).

We herein report a case of NT-AML, which showed a unique clinical course. Complete remission (CR) was achieved with a single administration of remission induction chemotherapy. Although consolidation chemotherapies were not available because of the patient’s critical condition, he had been in long-term remission for more than 40 months. However, repeated bone marrow examinations showed persistent clonal hematopoiesis with isolated del(20)(q12q13) without apparent myelodysplasia.

**Case Report**
A 62-year-old man was admitted to our hospital in January 2014 because of pancytopenia. He had developed dyspnea on exertion and palpitation three weeks before his admission. He had no remarkable past medical history. He had previously been a heavy smoker, but had quit smoking for several years. The patient was afebrile and did not complain of dyspnea in a resting state with ambient air. A physical examination revealed no enlarged superficial lymph nodes. The liver and spleen were not palpated. His lungs were clear and no abnormal cardiac sounds were heard on auscultation.

The white cell count was 2,500/μL with 22.5% neutrophils, 7.5% monocytes, 7.0% eosinocytes, 60.5% lymphocytes, and 2.5% blasts. The hemoglobin concentration was 4.8 g/dl, and the platelet count was 50,000/μL. The results of serum biochemistry tests were almost normal, with the

---

1Department of Hematology, Tenshi Hospital, Japan, 2Department of Gastroenterology, Tenshi Hospital, Japan and 3Department of Surgery, Tenshi Hospital, Japan

Received: March 1, 2017; Accepted: June 4, 2017; Advance Publication by J-STAGE: November 1, 2017

Correspondence to Dr. Tohru Takahashi, tohrut@cocoa.ocn.ne.jp
exception of the slight elevation of his lactate dehydrogenase (266 IU/L; reference range, 120-245) and C-reactive protein (3.92 mg/dl; reference range, ≤0.30) levels. A bone marrow examination disclosed the proliferation of extremely large blasts without granules or vacuoles in 49% of all nucleated cells (Fig. 1, 2). The large blasts were 4-5 times the size of red blood cells with prominent nucleoli. There were no apparent myelodysplastic changes. The blasts were negative for peroxidase staining or esterase staining. A cell surface marker analysis showed that the cells were positive for CD13, CD34 and HLA-DR (Fig. 3). This case was considered to have the minimally differentiated AML phenotype (FAB M0). A chromosomal analysis of the bone marrow cells showed 91, XXYY, -5, add(18)(p21),del(20)(q12q13)×2[11]/46,XY,del(20)(q12q13)[2] (Fig. 3).

Daunomycin (50 mg/m²) and cytarabine (100 mg/m²) were administered on day 1 and 2. However, high-grade fever developed on day 2, abruptly followed by severe cough and hypoxemia and chemotherapy was discontinued. Repeated blood and sputum cultures were negative, and the patient’s fever was unresponsive to antibiotics and anti-fungal agents. We suspected that the symptoms were caused by the destruction of leukemic cells and/or leukemic infiltration in the lungs. Daunomycin (on days 8 and 9), etoposide (50 mg/m², on days 10 and 11), and cytarabine (on days 8-10) were administered with corticosteroids. Even after the patient recovered from pancytopenia following chemotherapy, the white cell count increased to 3,970/μL on day 29 with serum KL-6 (a serum marker of interstitial pneumonitis) had been observed (up to 3,470 U/mL) throughout the clinical course. He was treated with daily oral prednisolone, and underwent total parenteral nutrition followed by tube feeding with gastrostomy. He slowly recovered from hypoxemia and muscle weakness, and was discharged in August 2014. He had been followed in our outpatient clinic, and his lung disease had been well controlled with oral steroids and the inhalation of a long-acting muscarinic receptor antagonist. However, left pneumothorax developed in September 2016 due to rapture of a bullae in the left upper lobe and he underwent partial upper left lung wedge resection.

Repeated bone marrow examinations showed no recurrence of AML, no apparent myelodysplastic changes, and pancytopenia had not developed since his discharge. However, the chromosomal analyses consistently showed an ab-

Figure 1. Bone marrow blasts. The large blasts were 4-5 times the size of red blood cells with prominent nucleoli.

The patient had suffered from general muscle weakness, difficulty swallowing, and hypoxemia with ambient air. The signs and symptoms resembled to those of critical illness polyneuropathy/myopathy, even though the patient had not been ventilated (7). Consolidation chemotherapies could not be administered, considering his critical condition. It was also suspected that the patient had an insidious lung disease, such as combined pulmonary fibrosis and emphysema before the onset of AML (8). The continuous elevation of the serum KL-6 (a serum marker of interstitial pneumonitis) had been observed (up to 3,470 U/mL) throughout the clinical course. He was treated with daily oral prednisolone, and underwent total parenteral nutrition followed by tube feeding with gastrostomy. He slowly recovered from hypoxemia and muscle weakness, and was discharged in August 2014. He had been followed in our outpatient clinic, and his lung disease had been well controlled with oral steroids and the inhalation of a long-acting muscarinic receptor antagonist. However, left pneumothorax developed in September 2016 due to rapture of a bullae in the left upper lobe and he underw
Figure 3. A cell surface marker analysis of the bone marrow blasts by flow cytometry. The cells were positive for CD13, CD34 and HLA-DR.

Figure 4. The chromosome analysis. 91,XXYY,-5, add (18)(p21),del(20)(q12q13) ×2.

normal karyotype with del(20)(q12q13) (Table). It should be noted that a clonal evolution with 46, XY,del(20)(q12q13),+21 was observed in May 2017. As of May 2017, he had been in remission and survived for more than 40 months.

Discussion

NT/T is a rare cytogenetic alteration in AML that accounts for <1% of AML (3). NT/T-AML is considered to be cytogenetically complex and is presumed to have an unfavorable prognosis. However, some reports have described a few NT/T-AML patients who experienced similar outcomes to intermediate-risk AML patients (1-3). Huang et al. reported that the median OS of their 38 NT/T-AML patients was 5 months (3). They divided their patients into two groups, namely those with a complex NT/T karyotype (an NT/T clone with ≥3 chromosomal abnormalities, either numerical or structural) and a non-complex karyotype (an NT/T clone with <3 chromosome abnormalities). Patients with the non-complex NT/T karyotype had a significantly superior OS in comparison to those with the complex NT/T karyotype (median OS, 10.7 versus 3.4 months). The current
case was categorized as a complex NT/T karyotype with an inferior OS according to their classification. Although the patient received only one course of remission induction chemotherapy due to severe comorbidities, he remained in complete remission for more than 40 months without any consolidation or maintenance therapies. Lemez et al. also reported a case of NT-AML with unusually long survival (80 months) (9). Some cases of NT/T-AML might have a better prognosis than generally expected.

It is presumed that tetraploidy represents later karyotypic changes that evolve from the initial chromosome or genetic changes that occur at the diploid stage. The previously reported duplication of chromosomal abnormalities such as the t(8;21) or t(15;17) in NT/T-AML cases might be offered as evidence of this hypothesis (10, 11). Huang et al. reported that the NT/T karyotype was detected during a relapsed/refractory state in 34% of NT/T-AML patients and 8 of 9 myelodysplastic syndrome (MDS) patients gained the NT/T karyotype at the time of transformation to AML (3). On the contrary, Jarosova et al. reported an NT/T-AML case in which 5q deletion was considered the secondary karyotypic change (12). In the present case, we considered that del(20)(q12q13) was an initial karyotypic change and a clonal evolution with NT occurred at the time of leukemic transformation.

Although the NT-AML clone was eradicated by chemotherapy, clonal hematopoiesis with an isolated del(20)(q12q13) persisted in our patient. MDS cases with isolated 20q deletion have been reported to show minimal morphological dysplasia and frequently present thrombocytopenia (13). They were reported to have a good prognosis and the median survival was reported to be 54 months in one study (14). The significance of isolated del(20)(q12q13) clones in our case was unclear. The patient had no cytopenia after discharge, and the repeated bone marrow examinations did not show any apparent myelodysplastic changes that were significant enough to be diagnosed as MDS. However, he might develop MDS in the future. Indeed, a clonal evolution with 46, XY,del(20)(q12q13),+21 was observed in May 2017; however there was no pancytopenia or apparent myelodysplasia.

Miyamoto et al. demonstrated that the acquisition of t(8;21) occurred in progenitors or hematopoietic stem cells and that the translocation was necessary, but not sufficient for leukemic transformation (15). Likewise, the acquisition of del(20)(q12q13) alone in our case might not have been sufficient for hematopoietic cancer transformation. Genovese et al. reported that clonal hematopoiesis with somatic mutations was readily detected by means of DNA sequencing, and that this became increasingly common as people age, and that it was associated with an increased risk of hema-

---

**Table. Chromosomal Analysis of Bone Marrow.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan. 2014</td>
<td>46,XXYY,-5,add(18)(q21),del(20)(q12q13)x2[11]/46,XY,del(20)(q12q13)[2]</td>
</tr>
<tr>
<td>May 2014</td>
<td>46,XY,del(20)(q12q13)[16]</td>
</tr>
<tr>
<td>Nov. 2014</td>
<td>46,XY,del(20)(q12q13)[20]</td>
</tr>
<tr>
<td>March 2016</td>
<td>46,XY,del(20)(q12q13)[20]</td>
</tr>
<tr>
<td>May 2017</td>
<td>46,XY,del(20)(q12q13)[16]</td>
</tr>
<tr>
<td></td>
<td>/46,XY,del(20)(q12q13),+21[4]</td>
</tr>
</tbody>
</table>
tologic cancer and death (16). Jaiswal et al. also reported that age-related clonal hematopoiesis was a common condition that was associated with increases in the risk of hematologic cancer (17). The clonal hematopoiesis with isolated del(20)(q12q13) in the present case might have been age related. Secondary genetic or epigenetic changes might have led to the transformation to NT-AML.

Although NT/T-AML cases have been generally considered to have a poor prognosis, some cases might have a relatively favorable course, for unpredictable reasons, as was observed in our case and others. The further study of more cases of NT/T-AML will be necessary to develop a better treatment strategy for this group of patients.

The authors state that they have no Conflict of Interest (COI).

References


The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).