Original Article

Molecular profiling of Chinese systemic anaplastic large cell lymphoma patients: novel evidence of genetic heterogeneity

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Background: Anaplastic large cell lymphoma (ALCL) is a rare non-Hodgkin lymphoma. A comprehensive understanding of the genetic and clinical heterogeneity of ALCL may help to improve the clinical management of patients with ALCL. However, due to the rarity of the disease, the genetic heterogeneity of ALCL has not been well elucidated. This study aimed to comprehensively elucidate the mutational landscape of tumor tissue samples from patients with systemic ALCL.

Methods: Thirty-six patients with systemic ALCL were enrolled in this retrospective study. Immunohistochemistry (IHC) was performed on tumor tissues at baseline to identify anaplastic lymphoma kinase (*ALK*) fusions. Capture-based targeted next-generation sequencing (NGS) with a panel spanning 112 lymphoma-related genes, including *ALK* rearrangements, was also performed on tumor tissue samples.

Results: A total of 102 mutations were identified in the entire cohort. Among the 36 patients included in this analysis, 14 (38.8%) were *ALK* positive, as determined by IHC, while NGS showed 12 patients (33.3%) to harbor *ALK* rearrangements. Younger patients were more likely to have *ALK*-positive ALCL (P=0.011). Patients with wild-type (WT) *ALK* were more likely to have single-nucleotide variants (SNVs) and insertions or deletions (INDELs) than patients with *ALK* rearrangements (P=0.027). Among the 22 patients with WT *ALK*, the most commonly mutated genes were *TP53* (n=6, 27.3%), followed by *NOTCH1* (n=5, 22.7%), *KMT2D* (n=3, 13.6%), *KRAS* (n=3, 13.6%), *TET2* (n=3, 13.6%), and *JAK1* (n=2, 9.1%). Mutations in *PRDM1*, a commonly mutated gene in *ALK*-negative patients, were not detected in our *ALK*-negative cohort. Start-loss of beta-2-microglobulin (*B2M*) was detected in another patient; this patient had a favorable prognosis, with an overall survival exceeding 19 months.

Conclusions: Our study revealed the unique genomic profiles of Chinese ALCL patients and represents an incremental step in deepening the understanding of the genetic heterogeneity of ALCL patients.

Keywords: Systemic anaplastic large cell lymphoma (systemic ALCL); somatic mutation; genetic heterogeneity; novel *ALK*-fusion

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Introduction

Anaplastic large cell lymphoma (ALCL) refers to a group of CD30-positive T-cell non-Hodgkin lymphomas (1,2). ALCL, which accounts for 13.8% of all peripheral T-cell lymphomas (PTCLs) (3), can be classified as primary cutaneous ALCL (pcALCL) and systemic ALCL. According to the World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues, systemic ALCL can be further divided based on anaplastic lymphoma kinase(*ALK*) status as *ALK*-negative ALCL and *ALK*-positive ALCL, the identification of which depends on either immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH) (1).

In recent years, gene rearrangement or overexpression of *ALK* has been considered to be a favorable prognostic biomarker for ALCL patients (4,5). Approximately half of the patients diagnosed with ALCL have ALK-positive status and have high response to standard chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone (CHOP) (6). Contrastingly, due to inefficacy of standard regimens, patients with *ALK*-negative ALCL often undergo more intensive therapies than *ALK*-positive ALCL patients (7-9). A growing number of studies have reported that the 5-year survival of a subset of *ALK*-negative ALCL patients with dual specificity phosphatase 22 (*DUSP22*) rearrangement was comparable to that of *ALK*-positive ALCL patients who received the same treatment regimen (9-11). Routine stem cell transplantation may lead to overtreatment for subsets of *ALK*-negative ALCL patients, such as those with *DUSP22* rearrangement, resulting in unnecessary increases in costs and risks for those patients. Rearrangements involving the tumor protein p63 (*TP63*) is considered to be a biomarker of poor prognosis for *ALK*-negative ALCL patients, with a 5-year survival rate of only 17% (10).

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for T-Cell lymphomas recommend that molecular analysis is used to detect *DUSP22* rearrangement if *ALK*-negative ALCL is diagnosed and follow the same recommended treatment regimen as that for *ALK*-positive patients (10-13). Illumination of the genetic and clinical heterogeneity of ALCL patients may facilitate improvements in the clinical management of ALCL patients. However, due to the rarity of ALCL, the genetic heterogeneity of this disease has not been well investigated. In this study, we retrospectively enrolled 36 systemic ALCL patients and performed genetic profiling of their tumor tissue samples using capture-based targeted next-generation sequencing (NGS) with a panel spanning 112 lymphoma-related genes, in order to elucidate the somatic profiles of ALCL patients with distinct clinical features. We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7574).

Methods

Patient and study design

This retrospective study included 36 patients who were diagnosed with systemic ALCL according to the WHO classification of Tumors of Hematopoietic and Lymphoid Tissue (2008) between January, 2015 and July, 2018 in Fujian Medical University Cancer Hospital and Fujian Cancer Hospital. All procedures involving human participants were performed in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Fujian Medical University Cancer Hospital and Fujian Cancer Hospital (approval number: 2017-055-01). Written informed consent was provided by all the patients included in the study.

Patient clinical data including age, sex, anatomic site, sites of extra nodal involvement, skin involvement during the disease course, disease stage, first-line treatment, treatment response, survival, and immunophenotype [CD3 antigen (CD3), Ki67 antigen (Ki67), BCL2 apoptosis regulator (BCL2), BCL6 transcription repressor (BCL6), or tumor necrosis factor (TNF) receptor superfamily member 8 (CD30)] were collected. Treatment response was assessed by the investigators according to the response evaluation criteria in lymphoma (RECIL) of the International Working Group (14). *ALK* status was detected by performing IHC. The threshold for immunopositivity was ≥20% of tumor cells (CD30 ≥80%). FISH was performed to detect *DUSP22* rearrangement. Capture-based targeted NGS with a panel spanning 112 lymphoma-related genes (Burning Rock Biotech, Cat. No. LK205) was performed on tissue samples collected at baseline. Overall survival (OS) was evaluated from the time of initial diagnosis to death, or last follow-up in surviving patients.

DNA extraction and library preparation

DNA was extracted from formalin-fixed paraffin-embedded

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(FFPE) tissue samples using a QIAamp DNA FFPE tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The DNA concentration was determined using the Qubit dsDNA assay (Life Technologies, Carlsbad, CA, USA). The M220 Focused-ultrasonicator (Covaris, Woburn, MA, USA) was used for DNA fragmentation, which was followed by end repair, phosphorylation, and adaptor ligation. DNA fragments of 200 to 400 bp were selected with AMPure beads (Agencourt AMPure XP kit; Beckman Coulter, Brea, CA, USA), and hybridization with capture probe baits, hybrid selection with magnetic beads, and polymerase chain reaction amplification were subsequently performed. A high-sensitivity DNA assay was used to examine the quality of the DNA (Bioanalyzer 2100; Agilent Technologies, Santa Clara, CA, USA). Indexed samples were sequenced using a Nextseq500 sequencer (Illumina, Inc., Hayward, CA, USA) with paired-end reads.

Sequencing data analysis

Sequencing data were mapped to the human genome (hg19) using Burrows-Wheeler aligner version 0.7.10 (15). Local alignment optimization, variant calling, and annotation were performed with GATK version 3.2 (Broad Institute, Cambridge, MA, USA) (16), and VarScan version 2.4.3 (Genome Institute, Washington University, Washington, DC, USA) (17). Loci with a depth of less than 100 were filtered out using the VarScan filter pipeline. At least five and eight supporting reads were required for insertions or deletions (INDELs) and single-number variations (SNVs), respectively. For all targeted regions, the aimed average sequencing depth was 2,000×. Variants with a population frequency >0.1% in public databases, including Exome Aggregation Consortium, 1,000 Genomes Project, ESP6500SI-V2 and dbSNP, were categorized as single-nucleotide polymorphisms (SNPs) and were excluded from further analyses. The ANNOVAR (18) and SnpEff version 3.6 (Wayne State University, Detroit, MI, USA) (19) softwares was used to annotate the remaining variants. Factera version 1.4.3 was employed for DNA translocation analysis (20).

Copy number variation (CNV) analysis was performed based on the depth of coverage data of capture intervals and corrected against sequencing bias resulting from GC content and probe design. The coverage of different samples was normalized to comparable scales based on the average coverage of all captured regions. The limits for CNV detection were 1.5 and 2.64 for deletions and amplifications, respectively.

Statistical analysis

All analyses were conducted in R, version 3.3.3 (http://www.R-project.org) and SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact tests and *t*-tests were performed. A two-sided P value of ≤0.05 was considered to show a statistically significant difference.

Results

Patient characteristics

The cohort was comprised of 67% males and 33% females with a median age of 38.5 years. Of the 36 ALCL patients evaluated by IHC, 14 were *ALK*-positive and 22 were *ALK*-negative. In three of the *ALK*-negative patients, *DUSP22* rearrangement was detected by FISH. Fifteen patients displayed extranodal involvement at diagnosis, and two patients had skin involvement during their disease course. Overall, 50% (n=18) of patients received a CHOP/CHOP-like regimen as the first-line treatment. A 15-year-old patient and a 13-year-old patient received BFM90 and BFM95 regimens, respectively. One patient underwent radiotherapy. Five patients did not receive any treatment, and the remaining 10 patients had no treatment information available. The median follow-up time was 26 months and the median overall survival was 42 months (range, 1–103 months). Demographic and clinical characteristics of the patients are shown in *Table 1*.

The mutation landscape of the entire cohort

Thirty-six patients with available baseline tumor tissue samples were included in the baseline mutation landscape analysis. A total of 102 mutations were identified from the entire cohort. The mutation landscape of the cohort is presented in *Figure 1A*. Mutations were detected in the tumor tissue samples of 81% (29/36) of patients. Twelve patients (33%) had *ALK* rearrangement, and one patient had an SNV of *ALK*. With IHC used as a reference, our capture-based targeted NGS had a sensitivity of 85.7% (12/14) and a specificity of 100% for identifying *ALK* status in biopsy samples. Two patients with *ALK* fusion detected by IHC were not identified by NGS. The tumor cell fraction in one of these samples was <30%, while the DNA from the other

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Table 1 Characteristics of patients

Characteristics	Num. (percentage)
Age (year)	
Median: 38.5 (3–81)	
Gender	
Female	12 (33.3)
Male	24 (66.7)
Ann Arbor stage	
I–II	7 (19.4)
III–IV	10 (27.7)
Missing	19 (52.8)
Extranodal involvement at diagnosis	
Yes	15 (41.7)
No	2 (5.6)
Missing	19 (52.8)
Skin involvement during disease course	
Yes	2 (5.6)
No	8 (22.2)
Missing	26 (72.2)
Initial treatment	
CHOP/CHOP-like	18 (50.0)
Others	3 (8.3)
None	5 (13.9)
Missing	10 (27.8)

CHOP, doxorubicin, cyclophosphamide, vincristine, prednisone.

sample was heavily degraded when NGS was performed. Among the 12 patients who had *ALK* rearrangements revealed by NGS, nucleophosmin 1 (NPM1) was the most common gene fusion partner, which was harbored by 7 (58%) patients. The other ALK gene fusion partners detected from the cohort included 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (*ATIC*)-*ALK* (n=2), trafficking from ER to Golgi regulator (*TFG*) (n=1), tropomyosin 3 (*TPM3*) (n=1), and myosin heavy chain 9 (*MYH9*) (n=1). Other commonly seen mutations included tumor protein p53 (*TP53*) (19.4%) and lysine methyltransferase 2D (*KMT2D*) (11.1%).

Compared with *ALK*-positive ALCLs, which have been well characterized at the molecular level, little is known about the genetic features of *ALK*-negative ALCLs. We compared the mutation landscape between patients with IHC-based *ALK*-negative and *ALK*-positive status. Patients with IHC-based *ALK*-negative status had significantly more SNVs and INDELs (P=0.027) (*Figure 1B*). Among the 22 IHC-based *ALK*-negative patients, the most common mutation was *TP53* (n=6, 27.3%), followed by notch receptor 1 (*NOTCH1*) (n=5, 22.7%), *KMT2D* (n=3, 13.6%), KRAS proto-oncogene, GTPase (*KRAS*) (n=3, 13.6%), TET methylcytosine dioxygenase 2 (*TET2*) (n=3, 13.6%), Janus kinase 1 (*JAK1*) (n=2, 9.1%), signal transducer and activator of transcription 3 (*STAT3*) (n=1, 4.5%), and Fas cell surface death receptor (*FAS*) (n=1, 4.5%). Of note, start-loss of beta-2-microglobulin (*B2M*) was detected in a 53-year-old *ALK*-negative patient (*Figure 2*) who was diagnosed with stage IIA ALCL with liver involvement at diagnosis and had no skin involvement during the disease course. This patient received a CHOP-like regimen as first-line treatment and achieved partial response, with progression-free survival and OS of 13 months and 93 months and counting, respectively. *DUSP22*-rearrangement, a favorable prognostic biomarker of *ALK*-negative ALCL, was detected in the same patient.

The correlation between ALK fusion status and various clinical parameters

The correlations between *ALK* fusion status and various clinical parameters were further investigated. *ALK*-positive ALCL was observed to be more common among younger patients (P=0.011), and *ALK*-negative patients were more likely to be CD3 positive (P=0.03) (*Figure 3*). No differences were observed between *ALK* fusion and Ki67 (P=0.64), sex (P=1), BCL2 (P=0.13), BCL6 (P=0.14), or disease stage (P=0.75).

Discussion

In this study, we revealed the somatic genomic landscapes of systemic ALCLs in 36 Chinese patients. We found that younger patients were more likely to be *ALK* positive, while patients with *ALK* wild-type (WT) ALCLs were more likely to have SNVs and INDELs than patients with *ALK* rearrangements. Overall, our study revealed new evidence of genetic heterogeneity between Chinese ALCL patients.

Due to the rarity of ALCL, the genetic and clinical heterogeneity of patients with the disease are not well understood. *ALK*-fusion is known to be more likely to occur in younger ALCL patients (4,7). The majority of

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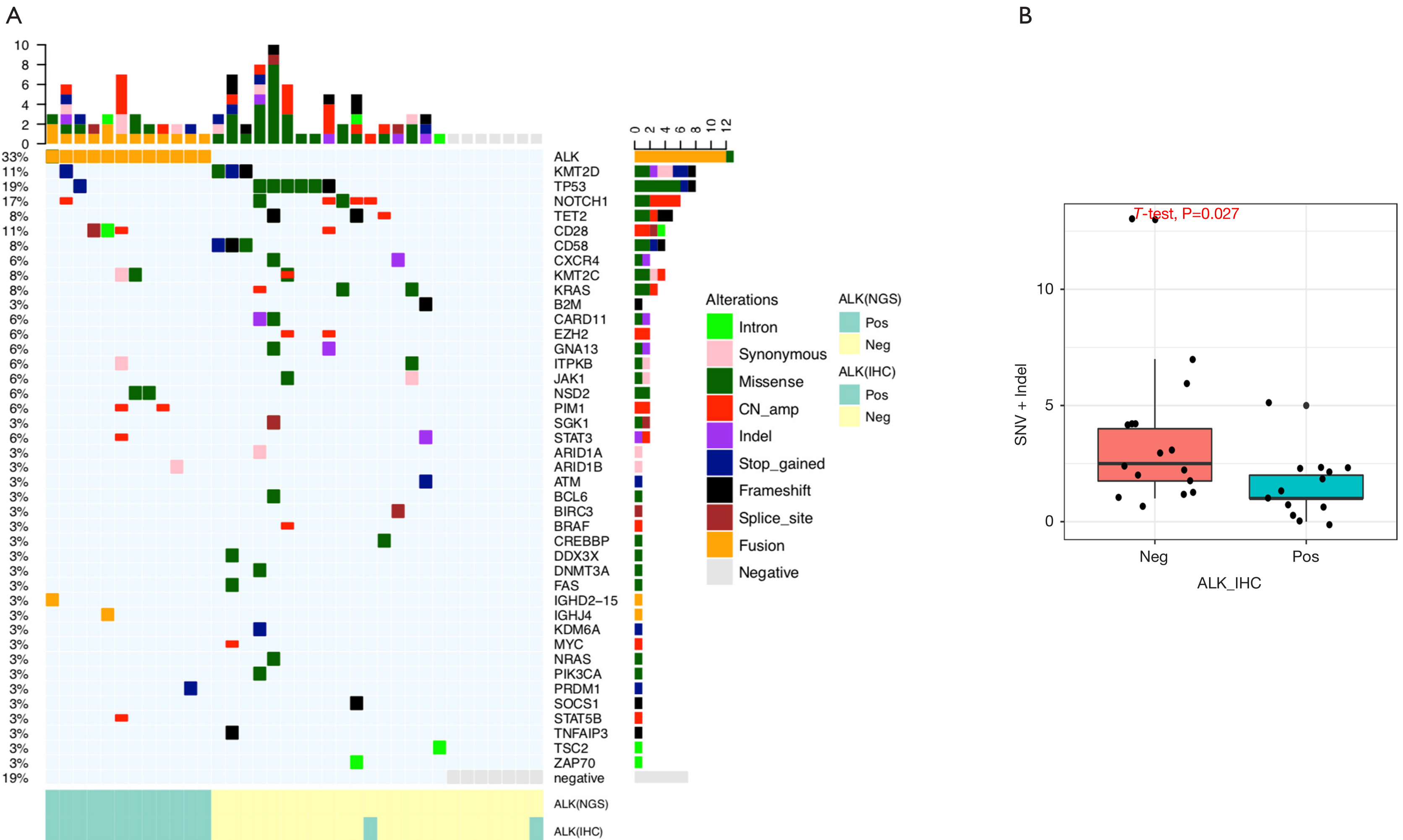

Figure 1 The mutation landscape of the cohort. (A) OncoPrint of mutations identified from tumor tissues at baseline. Different colors denote different types of mutations. Top bar represents the number of mutations harbored by a patient; side bar represents the number of patients carrying a certain mutation. Bottom bars provide information of anaplastic lymphoma kinase (*ALK*) status identified by next-generation sequencing (NGS) and immunohistochemistry (IHC). (B) Comparison of the total number of single nucleotide variations (SNV) and insertions or deletions (INDELs) based on the IHC-based ALK status of the patients.

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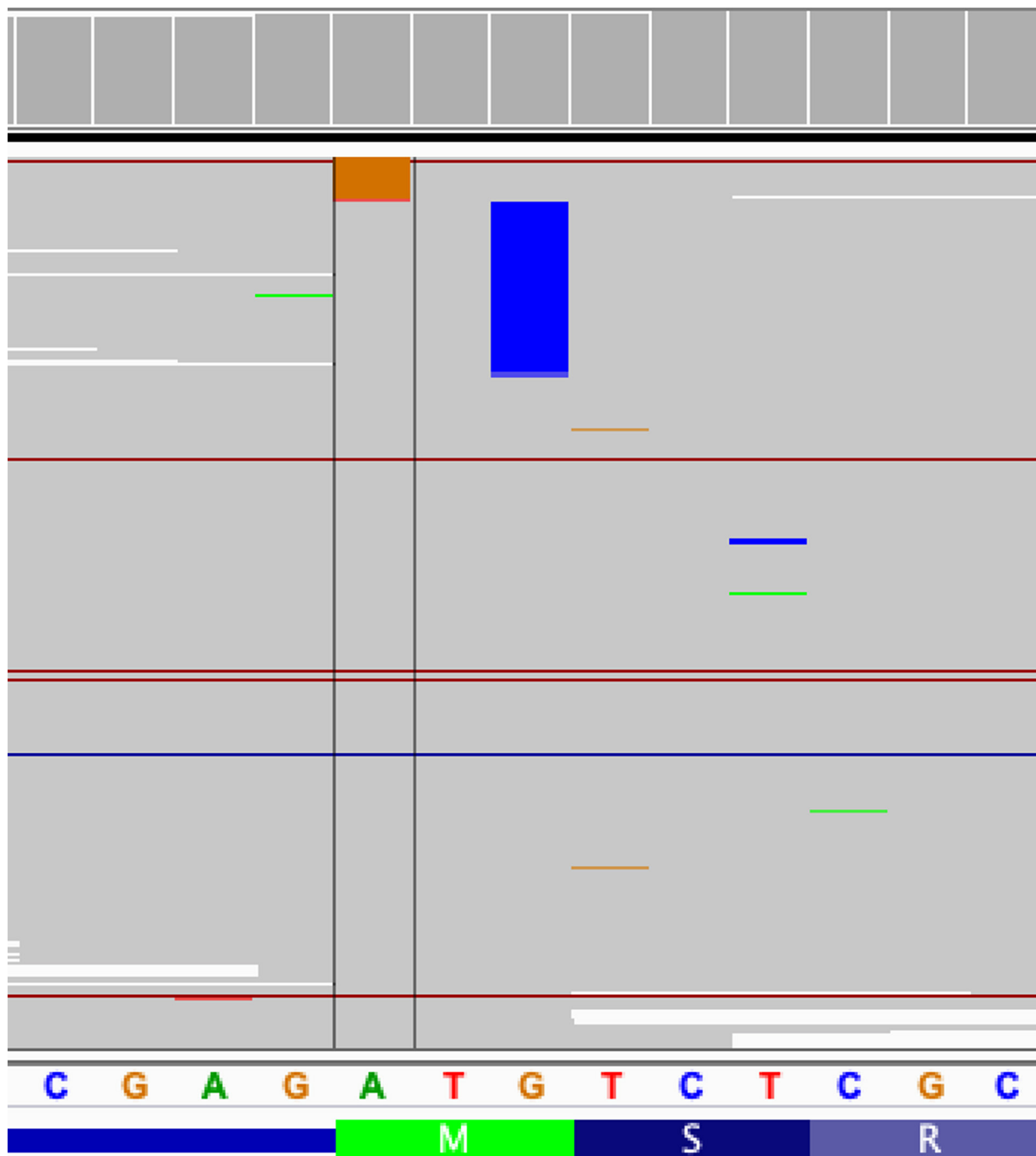

Figure 2 Allelic context of beta-2-microglobulin (*B2M*) in one patient. Next-generation sequencing analysis revealed start-loss of *B2M* (yellow and blue).

ALK-rearranged ALCLs have translocations involving the *ALK* gene and its partner *NPM1* (21). In the current cohort, the median age of the patients with *ALK*-positive ALCL was significantly younger than that of the *ALK*-negative patients. *NPM1-ALK* was the most common *ALK* rearrangement, which is consistent with the results of a previous study (21).

Compared with *ALK*-positive ALCLs, which are well

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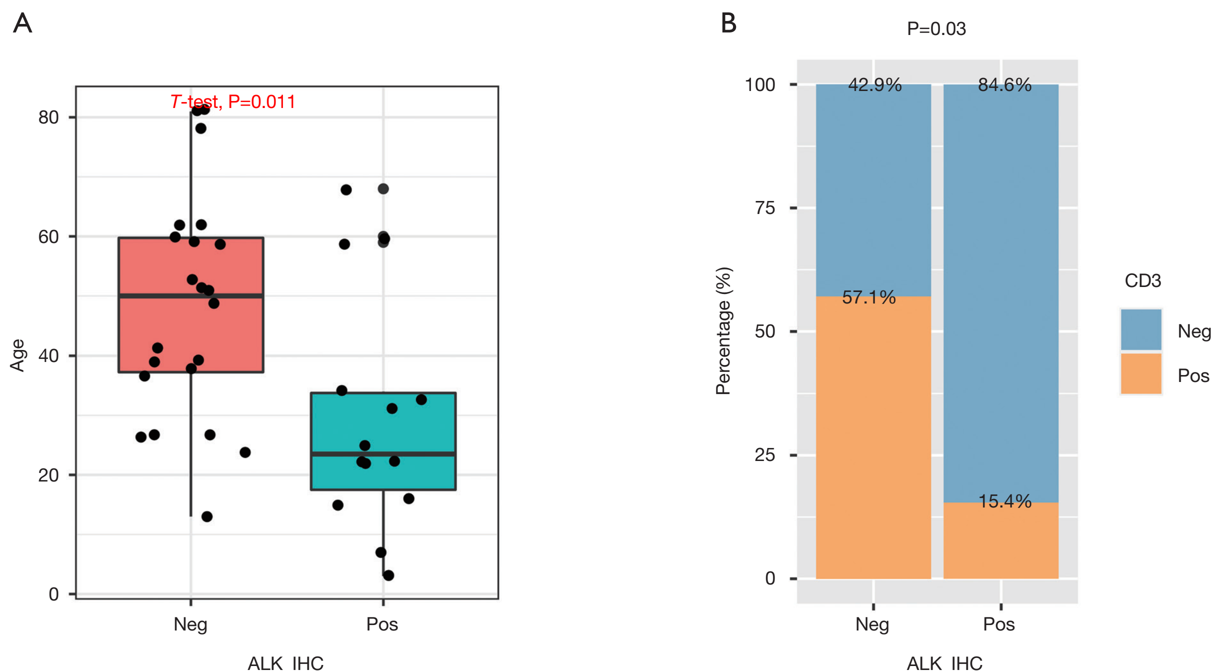

Figure 3 The correlations between anaplastic lymphoma kinase (*ALK*) fusion status and clinical parameters. (A) Patients with immunohistochemistry (IHC)-based *ALK* positive status were significantly younger as compared to *ALK*-negative patients. (B) Percentage of CD3-positive patients with different *ALK* status. The threshold for immunohistochemistry immunopositivity of CD3 was >20% of tumor cells.

characterized clinically, the genetic features of *ALK*-negative ALCLs are not well defined. Previous studies reported that the most commonly mutated genes in *ALK*-negative ALCL were *JAK1*, *STAT3*, PR/SET domain 1 (*PRDM1*), *TP53*, *TET2*, and *FAS* (22,23). The most common mutation among *ALK*-negative patients in our study was *TP53* (27.3%), followed by *NOTCH1* (22.7%), *KMT2D* (13.6%), *KRAS* (13.6%), *TET2* (13.6%), *JAK1* (9.1%), *STAT3* (4.5%), and *FAS* (4.5%). However, *PRDM1*, which has been reported as a common mutation in *ALK*-negative ALCL patients, was not detected in our *ALK*-negative cohort, which indicates that Chinese systemic ALCL patients may have a unique somatic mutational profile. Recently, chromosomal rearrangements of the *DUSP22* and *TP63* genes were reported in *ALK*-negative ALCL, with an incidence of 30% and 8%, respectively (10,24). In our study, however, *DUSP22* rearrangement was detected in three patients, accounting for only 13.6% of the *ALK*-negative ALCL patients; this discrepancy can be partly attributed to the small sample size. Detection of *TP63* rearrangement was not performed in our cohort.

In our study, start-loss of *B2M* gene was detected in one *ALK*-negative patient. This patient showed a favorable prognosis, with OS of 93 months and counting. Inactivating *B2M* mutations, including exon-1 splice-donor, start codon mutations, out-of-frame first-exon deletions, and acceptor-site mutations, may induce the loss of expression of the major histocompatibility complex class I complex, which is vital for antigen presentation (25). Inactivating *B2M* mutations have been detected in both Hodgkin and non-Hodgkin lymphoma patients. A lack of B2M expression is associated with a favorable prognosis in Hodgkin lymphoma patients; in contrast, it is associated with unfavorable prognosis in non-Hodgkin lymphoma patients (25,26). Low B2M (≤3 mg/dL) has also been reported to be a favorable prognostic factor in ALCL (27). To the best of our knowledge, our study provides the first evidence of start-loss of *B2M* in an ALCL patient, thus suggesting the prognostic value of *B2M* in ALCL. This patient harbored *DUSP22* rearrangement, which is a favorable prognostic biomarker of ALCL. Therefore, the prognostic value of *B2M* mutation needs to be further explored.

This study has some limitations. First, this is a retrospective study, which has all the drawbacks associated

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with a retrospective study including missing clinical data. Second, this study has a relatively small sample size, and limited clinical and follow-up data, which may have impacted the analyses. Third, this study was conducted in a single center that could introduce sample or population bias. Nevertheless, our study revealed the unique genomic profiles of Chinese systemic ALCL patients and represents an incremental step in improving the understanding of genetic heterogeneity in ALCL.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-7574

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures involving human participants were performed in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Fujian Medical University Cancer Hospital and Fujian Cancer Hospital (approval number: 2017-055-01). Written informed consent was provided by all the patients included in the study.

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