

# World Journal of *Clinical Cases*

*World J Clin Cases* 2020 May 6; 8(9): 1561-1755



**REVIEW**

- 1561 Nutrition management in acute pancreatitis: Clinical practice consideration  
*Lakananurak N, Gramlich L*

**MINIREVIEWS**

- 1574 Bone disease in chronic pancreatitis  
*Ahmed A, Deep A, Kothari DJ, Sheth SG*
- 1580 Role of microRNAs in the predisposition to gastrointestinal malignancies  
*Baz M, Ibrahim T*
- 1586 Recurrent anal fistulas: When, why, and how to manage?  
*Emile SH*

**ORIGINAL ARTICLE****Case Control Study**

- 1592 Removal of biofilm is essential for long-term ventilation tube retention  
*Ma Q, Wang H, Chen ZN, Wu YQ, Yu DZ, Wang PJ, Shi HB, Su KM*

**Retrospective Cohort Study**

- 1600 Neutrophil gelatinase-associated lipocalin does not predict acute kidney injury in heart failure  
*Ferrari F, Scalzotto E, Esposito P, Samoni S, Mistrorigo F, Rizo Topete LM, De Cal M, Virzi GM, Corradi V, Torregrossa R, Valle R, Bianzina S, Aspromonte N, Floris M, Fontanelli A, Brendolan A, Ronco C*
- 1608 Prognosis factors of advanced gastric cancer according to sex and age  
*Alshehri A, Alanezi H, Kim BS*

**Observational Study**

- 1620 Attitudes, knowledge levels and behaviors of Islamic religious officials about organ donation in Turkey: National survey study  
*Akbulut S, Ozer A, Firinci B, Saritas H, Demyati K, Yilmaz S*
- 1632 Serotonin transporter and cholecystokinin in diarrhea-predominant irritable bowel syndrome: Associations with abdominal pain, visceral hypersensitivity and psychological performance  
*Qin G, Zhang Y, Yao SK*

## CASE REPORT

- 1642** Cholesteryl ester storage disease of clinical and genetic characterisation: A case report and review of literature  
*Rashu EB, Junker AE, Danielsen KV, Dahl E, Hamberg O, Borgwardt L, Christensen VB, Wewer Albrechtsen NJ, Gluud LL*
- 1651** Seroconversion of HBsAG coincides super-infection with hepatitis A: A case report  
*Beisel C, Addo MM, zur Wiesch JS*
- 1656** Liver cirrhosis in a child associated with Castleman's disease: A case report  
*Kobayashi S, Inui A, Tsunoda T, Umetsu S, Sogo T, Mori M, Shinkai M, Fujisawa T*
- 1666** Granulocyte colony-stimulating factor-producing squamous cell carcinoma of the tongue exhibiting characteristic fluorine-18 deoxyglucose accumulation on positron emission tomography-computed tomography: A case report  
*Shimamoto H, Hirota Y, Kashima Y, Kinoshita N, Yokokawa M, Ikeda T, Harada H*
- 1674** Expander implantation for correction of high-riding nipple with enlarged nipple-areola complex using revision mastopexy: A case report  
*Qin F, Yu NZ, Yang E, Zeng A, Hao Y, Zhu L, Wang XJ*
- 1679** Pyoderma gangrenosum confused with congenital preauricular fistula infection: A case report  
*Zhao Y, Fang RY, Feng GD, Cui TT, Gao ZQ*
- 1685** Central nervous system relapse in a pediatric anaplastic large cell lymphoma patient with CLTC/ALK translocation treated with alectinib: A case report  
*Yang J, Li J, Gu WY, Jin L, Duan YL, Huang S, Zhang M, Wang XS, Liu Y, Zhou CJ, Gao C, Zheng HY, Zhang YH*
- 1693** Colonic perforation in a nasopharyngeal carcinoma patient treated with fluorouracil: A case report  
*Lu WJ, Li G, Gao L*
- 1698** Thoracoscopic resection of a huge esophageal dedifferentiated liposarcoma: A case report  
*Ye YW, Liao MY, Mou ZM, Shi XX, Xie YC*
- 1705** COVID-19 managed with early non-invasive ventilation and a bundle pharmacotherapy: A case report  
*Peng M, Ren D, Liu XY, Li JX, Chen RL, Yu BJ, Liu YF, Meng X, Lyu YS*
- 1713** Application of curved ablation in liver cancer with special morphology or location: Report of two cases  
*Cao N, Cai HJ, Sun XX, Liu DL, Huang B*
- 1721** Giant ventral hernia simultaneously containing the spleen, a portion of the pancreas and the left hepatic lobe: A case report  
*Luo XG, Lu C, Wang WL, Zhou F, Yu CZ*

- 1729** Endoscopic ultrasonography elastography in the diagnosis of intrapancreatic ectopic spleen: A case report  
*Ge N, Sun SY*
- 1735** Mesonephric adenocarcinoma of the uterine cervix with rare lung metastases: A case report and review of the literature  
*Jiang LL, Tong DM, Feng ZY, Liu KR*
- 1745** Portal hypertension in a patient with biliary hamartomas: A case report  
*Li QQ, Guo XZ, Li HY, Qi XS*

**LETTER TO THE EDITOR**

- 1752** Rare primary lymphoepithelioma-like carcinoma of the renal pelvis  
*Lai SC, Seery S, Diao TX, Wang JY, Liu M*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Paul E Sijens, PhD, Associate Professor, Department of Radiology, University Medical Center Groningen and University of Groningen, Groningen 9713 GZ, Netherlands

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

*WJCC* mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJCC* as 1.153 (5-year impact factor: N/A), ranking *WJCC* as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Yan-Xia Xing*  
 Proofing Production Department Director: *Yun-Xiaojuan Wu*  
 Responsible Editorial Office Director: *Jin-Lei Wang*

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Semimonthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

May 6, 2020

**COPYRIGHT**

© 2020 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Central nervous system relapse in a pediatric anaplastic large cell lymphoma patient with CLTC/ALK translocation treated with alectinib: A case report

Jing Yang, Jun Li, Wei-Yue Gu, Ling Jin, Yan-Long Duan, Shuang Huang, Meng Zhang, Xi-Si Wang, Yi Liu, Chun-Ju Zhou, Chao Gao, Hu-Yong Zheng, Yong-Hong Zhang

**ORCID number:** Jing Yang (0000-0002-1455-4253); Jun Li (0000-0001-7232-0036); Wei-Yue Gu (0000-0002-7551-2006); Ling Jin (0000-0001-7148-141X); Yan-Long Duan (0000-0003-2048-6397); Shuang Huang (0000-0002-7967-9743); Meng Zhang (0000-0002-9695-5279); Xi-Si Wang (0000-0002-0565-6530); Yi Liu (0000-0002-7041-305X); Chun-Ju Zhou (0000-0002-5664-3190); Chao Gao (0000-0001-6652-5457); Hu-Yong Zheng (0000-0002-6220-2789); Yong-Hong Zhang (0000-0003-1960-3349).

**Author contributions:** Zheng HY, Zhang YH, and Yang J designed the study; Li J, Gu WY, Liu Y, Zhou CJ, and Gao C performed the experiments; Yang J, Li J, Duan YL, Huang S, Zhang M, and Wang XS collected the data and samples; Yang J, Li J, and Gao C wrote the manuscript; Zheng HY and Zhang YH reviewed the final manuscript and take primary responsibility for the article; all authors read and approved the final manuscript.

**Supported by** the Special Fund of the Pediatric Medical Coordinated Development Center of Beijing Hospitals Authority, No. XTZD20180204.

**Informed consent statement:** Informed written consent was obtained from the patient and her parents for publication of this report and the accompanying images.

**Conflict-of-interest statement:** The

**Jing Yang, Jun Li, Ling Jin, Yan-Long Duan, Shuang Huang, Meng Zhang, Xi-Si Wang, Yi Liu, Chun-Ju Zhou, Chao Gao, Hu-Yong Zheng, Yong-Hong Zhang,** Beijing Key Laboratory of Pediatric Hematology Oncology, National Discipline of Pediatrics, Ministry of Education, MOE Key Laboratory of Major Diseases in Children; Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China

**Wei-Yue Gu,** Chigene (Beijing) Translational Medical Research Center Co., Ltd., Beijing 101111, China

**Corresponding author:** Hu-Yong Zheng, MD, PhD, Beijing Key Laboratory of Pediatric Hematology Oncology, National Discipline of Pediatrics, Ministry of Education, MOE Key Laboratory of Major Diseases in Children; Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, No. 56, Nanlishi Road, Beijing 100045, China. [zhenghuyong@vip.sina.com](mailto:zhenghuyong@vip.sina.com)

### Abstract

#### BACKGROUND

The aberrant expression of the anaplastic lymphoma kinase (*ALK*) gene in *ALK*-positive (*ALK*+) anaplastic large cell lymphoma (ALCL) is usually due to t(2;5)/NPM-*ALK*. However, rarely, aberrant *ALK* expression can also result from a rearrangement of the *ALK* gene with various partner genes. Central nervous system (CNS) metastasis is very rare in *ALK*+ALCL. Patients with CNS involvement show an inferior prognosis.

#### CASE SUMMARY

Here, we present the case of an 8-year-old girl diagnosed with *ALK*+ALCL. She presented with fever, skin nodules, leg swelling, and abdominal pain over the preceding 6 mo. She had extensive involvement and showed an extraordinary rare translocation, t(2;17)/CLTC-*ALK*, as demonstrated by RNA-seq. She underwent chemotherapy as per ALCL99, followed by vinblastine (VBL) maintenance treatment, and achieved complete remission. However, she developed CNS relapse during VBL monotherapy. The patient achieved a durable second remission with high-dose chemotherapy (including methotrexate 8 g/m<sup>2</sup>) and continuous treatment with alectinib and VBL.

authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited Manuscript

**Received:** January 16, 2020

**Peer-review started:** January 16, 2020

**First decision:** March 27, 2020

**Revised:** April 8, 2020

**Accepted:** April 21, 2020

**Article in press:** April 21, 2020

**Published online:** May 6, 2020

**P-Reviewer:** Cihan YB

**S-Editor:** Ma YJ

**L-Editor:** Wang TQ

**E-Editor:** Wu YXJ



## CONCLUSION

Alectinib showed significant and durable CNS effects in this patient. However, more cases are needed to prove the efficacy and safety of alectinib for pediatric ALK+ALCL patients.

**Key words:** Anaplastic; Lymphoma; Pediatric; CLTC/ALK; Central nervous system; Alectinib; Case report

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Both CLTC-anaplastic lymphoma kinase translocation and central nervous system (CNS) metastasis are very rare in anaplastic large cell lymphoma. This paper reports a rare pediatric case of anaplastic large cell lymphoma with the CLTC-anaplastic lymphoma kinase fusion gene. The patient had an aggressive clinical course and underwent CNS relapse during treatment. The current patient achieved sustained complete remission with chemotherapy and alectinib. Alectinib conferred significant and durable CNS effects in this patient.

**Citation:** Yang J, Li J, Gu WY, Jin L, Duan YL, Huang S, Zhang M, Wang XS, Liu Y, Zhou CJ, Gao C, Zheng HY, Zhang YH. Central nervous system relapse in a pediatric anaplastic large cell lymphoma patient with CLTC/ALK translocation treated with alectinib: A case report. *World J Clin Cases* 2020; 8(9): 1685-1692

**URL:** <https://www.wjgnet.com/2307-8960/full/v8/i9/1685.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v8.i9.1685>

## INTRODUCTION

Anaplastic lymphoma kinase (ALK) expression is absent from all normal human postnatal tissues except rare cells in the brain. Expression of the *ALK* gene in ALK-positive (ALK+) anaplastic large cell lymphoma (ALCL) is usually due to the (2;5)(p23;q35) chromosome translocation, which causes the fusion of the *ALK* and *NPM1* genes, providing a promoter involved in the activation of ALK kinase, which plays a direct causative role in ALCL<sup>[1,2]</sup>.

The aberrant expression of ALK can also result from a rearrangement of the *ALK* gene with various partner genes<sup>[2-4]</sup>. The ALK fusion partner determines the intracellular localization of the fusion protein. Immunohistochemistry with specific anti-ALK monoclonal antibodies indicates that NPM1-ALK fusion proteins are characterized by nuclear and cytoplasmic ALK staining, whereas the variant ALK fusion proteins are usually cytoplasmic and rarely show membranous ALK staining. Thus, immunohistochemistry can be used for screening the classical (2;5) translocation instead of molecular tests<sup>[1]</sup>.

*CLTC-ALK* is a known recurrent fusion gene in ALK-positive diffuse large B-cell lymphoma but very rare in ALCL<sup>[2,5-7]</sup>. Here, we report a case of ALCL with *CLTC-ALK* gene fusion arising from t(2;17)(p23;q23). The patient developed central nervous system (CNS) metastasis and achieved complete remission (CR) through chemotherapy and treatment with alectinib, which is a second-generation ALK tyrosine kinase inhibitor (TKI). This study was approved by the Beijing Children's Hospital Institutional Ethics Committee.

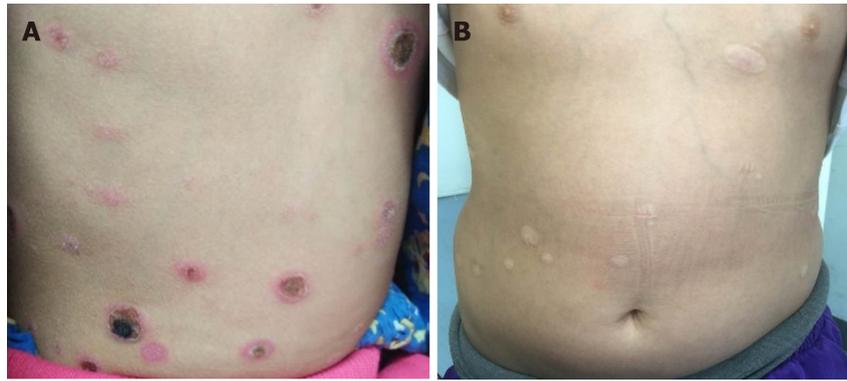
## CASE PRESENTATION

### Chief complaints

An 8-year-old girl presented with fever, skin nodules with necrosis and ulceration, leg swelling, and abdominal pain over the preceding 6 mo (Figure 1).

### Imaging examinations

She was admitted to our institution, and magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) scans revealed that she had extensive involvement, including the skin, soft tissues, lungs, bones (skull, vertebrae, ribs, ilium, limb bones, and jawbone), bone marrow, lymph nodes



**Figure 1** Skin rashes (A) before treatment and (B) after chemotherapy.

(cervical, mediastinal, axillary, pelvic, and inguinal lymph nodes), ovaries, and pancreas, as well as a massive mesenteric tumor (Figure 2).

#### **Laboratory examinations**

Complete blood count showed mild anemia (hemoglobin 9.9 g/dL), while the white blood cell and platelet counts were normal. Lactose dehydrogenase was slightly elevated (720 IU/L). A bone marrow aspiration smear revealed 86% of atypical lymphocytes, which differed in size and shape. They had eccentric nuclei, prominent nucleoli, and abundant cytoplasm containing prominent vacuoles (Figure 3).

#### **Pathological findings**

Histopathological examination of the biopsied specimens from inguinal lymph nodes and bone marrow showed a diffuse infiltrate of irregularly shaped tumor cells. Immunophenotypically, the tumor cells were negative for CD3, CD5, CD8, and CD20, and positive for CD30, CD4, CD7, CD2, EMA, TIA-1, Gram-B, and Ki67 (80%+); ALK was strongly positive. Therefore, a diagnosis of ALK+ALCL was made. Rarely, the ALK protein was distributed in a restricted cytoplasmic staining pattern, indicating that the aberrant ALK expression was due to a partner gene other than *NPM1* (Figure 4).

#### **Further diagnostic work-up**

Transcriptome sequencing of bone marrow mononuclear cells (BMMCs) by RNA-seq was performed to identify the fusion gene. Total RNA was extracted with TRIzol reagent. The transcriptome was constructed using the TruSeq Stranded mRNA library kit (Illumina, San Diego, CA, United States), and the library containing 200bp fragments was paired-end sequenced in duplicate with the Illumina HiSeq X Ten platform. Sequencing data were filtered and quality controlled to obtain clean data and aligned to the hg19 reference genome and its transcriptome. Differential gene expression ( $\log_2$  fold change > 1 and FDR < 0.01) and its enrichment were obtained. SNP/InDel calling, annotation, and fusion gene analysis were subsequently performed using biostatistical software. A genetic variation of transcriptional fusion was identified with mutation point A in chr17:57768072 and mutation point B in chr2:29448328. We also confirmed the *CLTC-ALK* fusion by reverse transcription-polymerase chain reaction (RT-PCR). Total RNA was extracted from BMMCs and then reverse transcribed into cDNA. To amplify *CLTC-ALK*, two rounds of PCR were performed; the amplification conditions and primer sequences were as previously reported<sup>[8]</sup> (Figure 5).

---

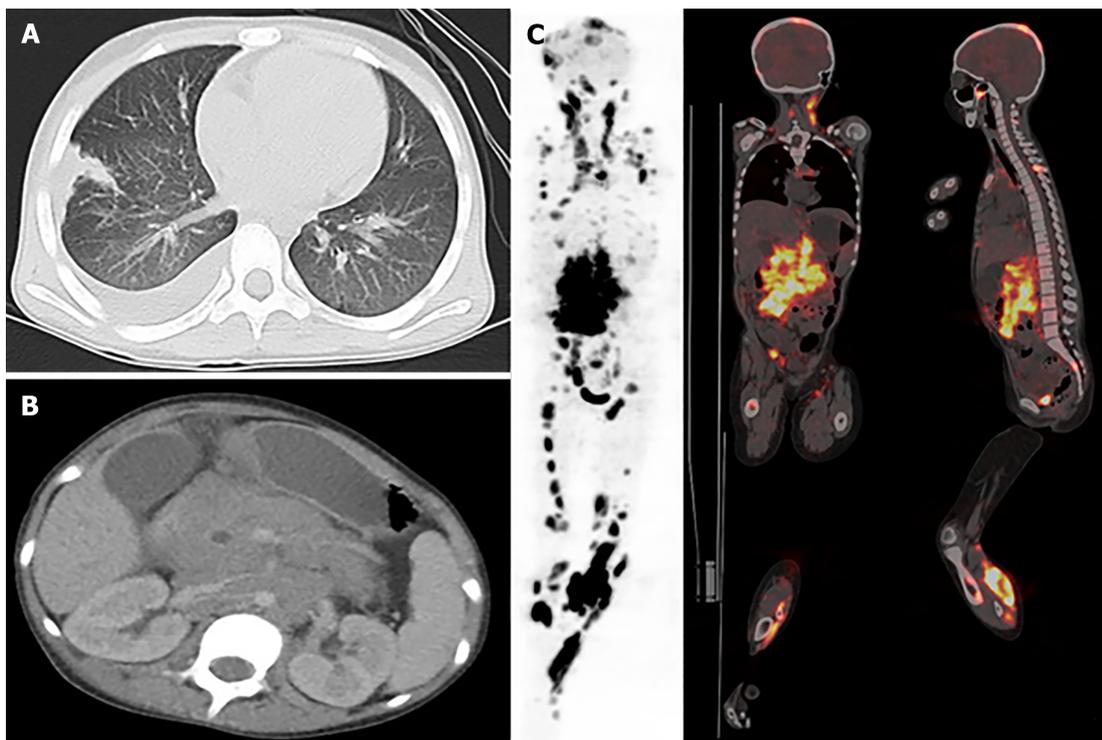
## **FINAL DIAGNOSIS**

ALK-positive ALCL with *CLTC-ALK* fusion gene was found. According to the St Jude Children's Research Hospital staging system, the disease was stage IV.

---

## **TREATMENT**

The patient underwent chemotherapy as per the ALCL99 protocol<sup>[9]</sup> and showed a good response. PET-CT, performed after six courses of chemotherapy, indicated that there were only residual tumors in her left lower extremity. We also detected



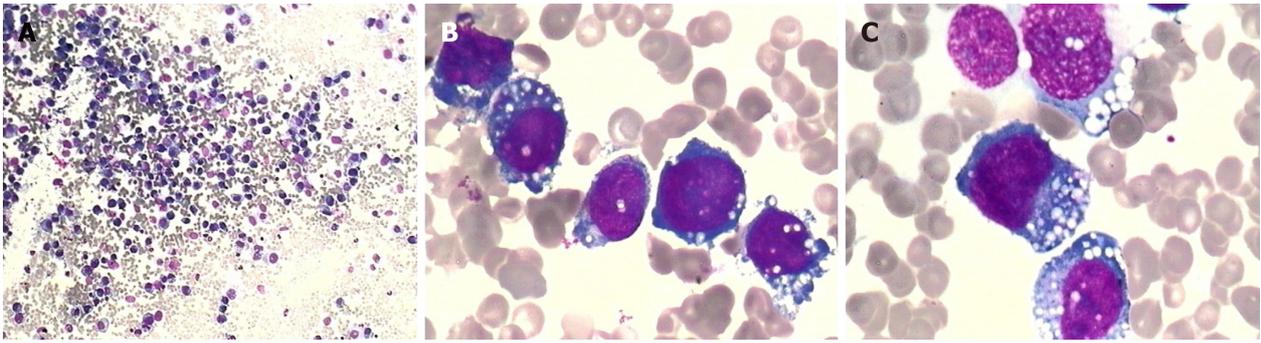
**Figure 2** Images at diagnosis. A and B: Computed tomography of the chest (A) and abdomen (B); C: Positron emission tomography/computed tomography scan of the whole body.

CLTC/ALK expression in her bone marrow (BM) and peripheral blood (PB) samples at follow-up by nested PCR. The outcome was still positive. Then, she received weekly vinblastine (VBL) injections as maintenance treatment, at an initial dose of 6 mg/m<sup>2</sup> (maximum, 10 mg) per injection, which was then reduced to 5 mg/m<sup>2</sup> for grade 4 neutropenia. Three months later, she achieved CR, and CLTC/ALK was undetectable in her BM and PB samples.

However, 1 mo later, she developed fever and headache and had frequent generalized seizures. The left pupil was dilated and did not react to light or accommodation. The cerebral spinal fluid (CSF) was slightly yellow (Figure 6Aa); CSF glucose level was 0.04 mmol/L, and CSF protein level was 4.5 g/L. A cytospin of CSF revealed approximately 72 tumor cells/high-power field (Figure 6Ab). MRI images of the brain revealed new lesions in the cerebral hemisphere, basal ganglia, thalamus, and brainstem. Intracranial segments of the bilateral optic nerves were enlarged (Figure 6Ba). Besides the CNS, there were no other signs of tumor relapse on CT and MRI scans. CLTC/ALK was positive again in one BM sample.

Two intrathecal triple therapies were administered, but the patient's condition did not improve. More intensive chemotherapy and ALK-directed kinase inhibitor therapy were considered. She underwent treatment with both chemotherapy of COPADM according to LMB89 group C (including MTX 8 g/m<sup>2</sup>) and alectinib given orally<sup>[10]</sup>. There is no information on alectinib use in pediatrics; the dose was extrapolated from the recommended adult dose (600 mg twice daily). Given the patient's weight (34 kg) and body surface area (1.20 m<sup>2</sup>), alectinib was commenced at a total daily dose of 750 mg (divided into two doses). Written informed consent was obtained from her parents before commencing alectinib treatment.

Her fever resolved within one day; no seizures occurred thereafter. She received triple intrathecal therapy on the second day of chemotherapy. The CSF was much clearer than before, and no tumor cell was found on CSF cytospin. During the chemotherapy, complication by sepsis due to *Escherichia coli* and grade 4 neutropenia were observed. After the sepsis was cured, she received three more courses of chemotherapy of COPADM (MTX 8 g/m<sup>2</sup>), CYVE, and HD-MXT (5 g/m<sup>2</sup>) sequentially, with simultaneous alectinib. Thereafter, evaluation revealed that the involvement of the brain parenchyma and optic nerves was reduced (Figure 6Bb). She was discharged and started with maintenance treatment of VBL and alectinib at the clinic. The total daily dose of alectinib was reduced to 450-600 mg due to grade 4 neutropenia. The alectinib plasma trough level (C<sub>min</sub>) was monitored, and it ranged from 250 to 427 ng/mL. Two months later, she achieved CR, as shown by brain MRI (Figure 6Bc). CLTC/ALK was negative again in the BM and PB samples. Allogeneic



**Figure 3** Wright-Giemsa-stained bone marrow smear. A: 100 ×; B and C: 1000 ×. Anaplastic lymphoma cells differed in size and shape. They had eccentric nuclei, prominent nucleoli, and abundant cytoplasm containing prominent vacuoles.

hematopoietic stem cell transplantation was suggested, but it was declined by her parents.

## OUTCOME AND FOLLOW-UP

Thus far, she has completed treatment with VBL and alectinib for 17 mo. The treatment was tolerated well, without significant adverse effects, except grades 1-4 neutropenia. She is still in CR, but her vision has not recovered.

## DISCUSSION

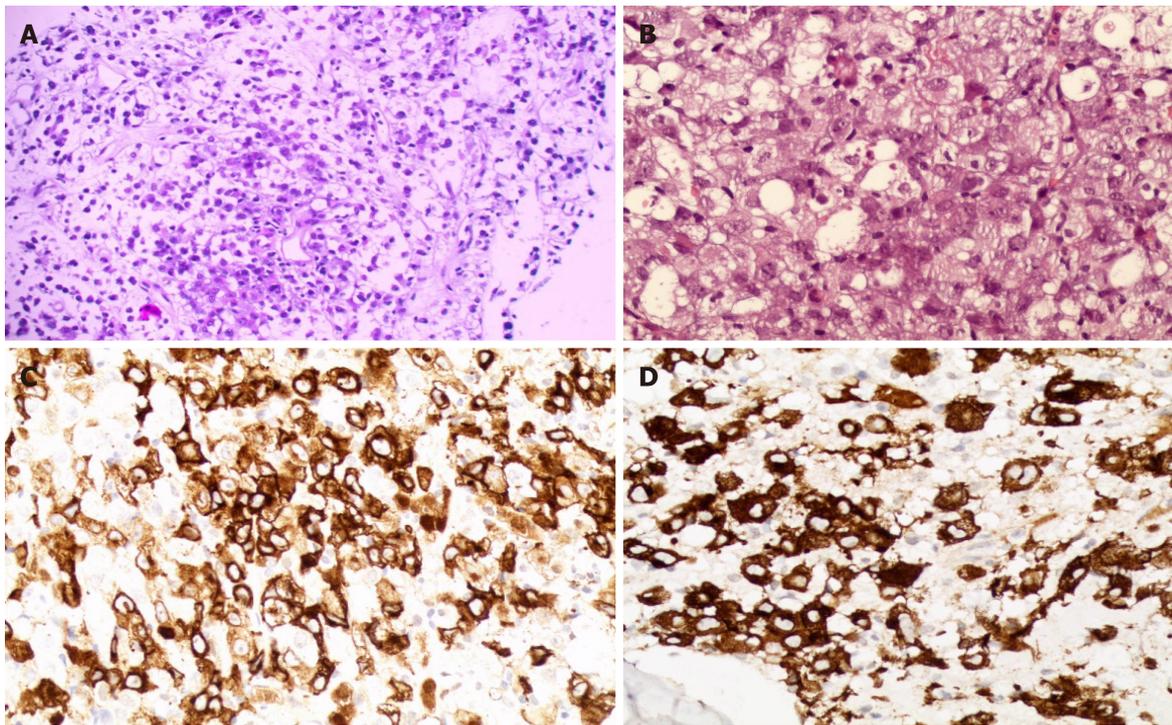
Here, we present an extraordinary and rare case of ALCL with the *CLTC-ALK* fusion gene. The clinical relevance of various translocations has not been confirmed. Five X-ALK variants have been reported to display different proliferative, migratory, and invasive properties, which seem to be due to differential activation of various signaling pathways<sup>[11]</sup>. This patient's invasive and refractory clinical process suggests the possibility of a more aggressive property related to the *CLTC/ALK* variant in ALCL, although more cases are needed to confirm this.

VBL has shown remarkable activity as a single agent even in the treatment of relapsed ALCL<sup>[12]</sup>. There are limited data on VBL passing the blood-brain barrier (BBB). Besides this patient, there are other reports on CNS progression during VBL therapy for high-risk ALK+ALCL<sup>[13]</sup>. These cases indicate that the CNS/CSF penetration of VBL is insufficient for the control of high-risk ALCL relapse, and CNS-directed therapy ought to be considered during VBL monotherapy.

The reported incidence of CNS involvement in ALK+ALCL is about 2.6%. Patients with CNS involvement show an inferior prognosis<sup>[9]</sup>. The first-generation ALK-inhibitor crizotinib has poor CSF penetrance. Alectinib is not a P-glycoprotein substrate; hence, it could penetrate the BBB<sup>[14]</sup>. The reported CSF penetration rates of crizotinib and alectinib are 0.26% and 86%, respectively<sup>[15]</sup>. Alectinib has demonstrated potent CNS activity in ALK-positive non-small-cell lung cancer patients<sup>[16,17]</sup>. It also showed good CNS response in two reported ALK+ALCL patients with CNS involvement<sup>[18,19]</sup>. However, pediatric dosing data are lacking. A population pharmacokinetic analysis showed that a higher-than-median steady-state alectinib C<sub>min</sub> of ≥ 435 ng/mL is associated with a greater reduction in tumor size<sup>[20]</sup>. The current patient did not reach this target concentration because of grade 3 or 4 neutropenia. We speculate that this might be related to the co-administration of VBL, which can also cause myelosuppression. Nonetheless, the disease was still well controlled, and no significant adverse events occurred.

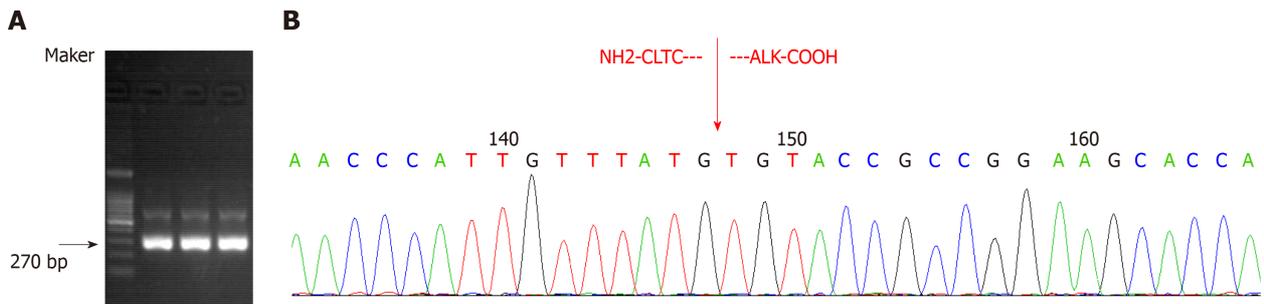
## CONCLUSION

In summary, this report describes a rare pediatric ALCL patient with the *CLTC-ALK* fusion gene. After CNS relapse, she achieved a durable second remission with high-dose chemotherapy and continuous alectinib. Alectinib showed significant and durable CNS effects in this patient. To our knowledge, this is the first published pediatric case report describing the use of alectinib for the treatment of ALK+ALCL. However, our findings are based on a single patient, and more cases are needed to

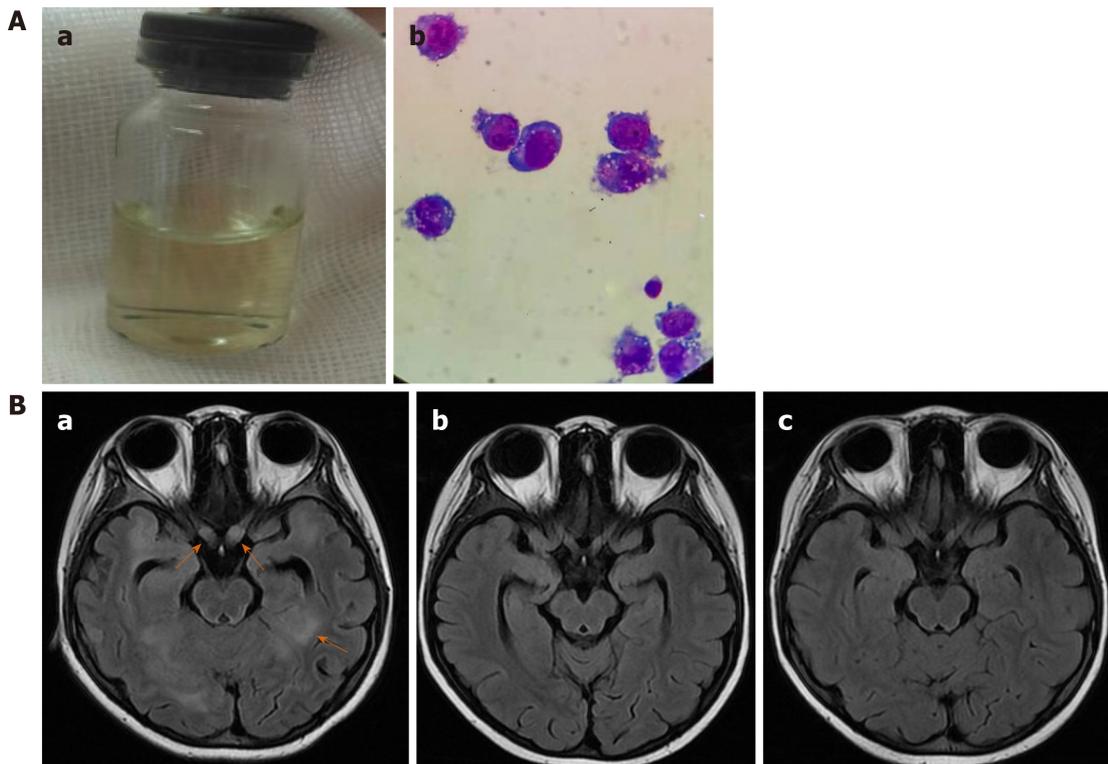


**Figure 4** Histological and immunophenotypic results. A: Hematoxylin–eosin-stained section of a lymph node; B: Hematoxylin–eosin-stained section of bone marrow biopsy; C: Positive CD30 staining; D: Positive ALK staining in a cytoplasmic pattern.

prove the efficacy and safety of alectinib for pediatric patients.



**Figure 5** The sample at the diagnosis time-point showing the expected 270 bp *CLTC-ALK* reverse transcription-polymerase chain reaction product (three bands represent three repetitions) (A) and direct sequencing results of polymerase chain reaction products (B). The arrow shows the translocation breakpoint (B).



**Figure 6** Central nervous system recurrence after 13 mo of treatment. A: Yellow cerebral spinal fluid (a) and tumor cells on cytospin of cerebral spinal fluid (b); B: Magnetic resonance imaging images. a: New lesions in the brain parenchyma and enlarged bilateral optic nerves; b: The involvement of the brain and optic nerves shrank after 2 mo of chemotherapy and alectinib treatment; c: Complete remission after 4 mo of treatment.

## ACKNOWLEDGEMENTS

The authors would like to thank the patient and her family.

## REFERENCES

- 1 **Stein H**, Foss HD, Dürkop H, Marafioti T, Delsol G, Pulford K, Pileri S, Falini B. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. *Blood* 2000; **96**: 3681-3695 [PMID: 11090048 DOI: 10.1053/beh.2000.0100]
- 2 **Swerdlow SH**, Campo E, Harris NL. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th edition). IARC: Lyon, 2017
- 3 **De Paep P**, Baens M, van Krieken H, Verhasselt B, Stul M, Simons A, Poppe B, Laureys G, Brons P, Vandenberghe P, Speleman F, Praet M, De Wolf-Peters C, Marynen P, Wlodarska I. ALK activation by the *CLTC-ALK* fusion is a recurrent event in large B-cell lymphoma. *Blood* 2003; **102**: 2638-2641 [PMID: 12750159 DOI: 10.1182/blood-2003-04-1050]
- 4 **Touriol C**, Greenland C, Lamant L, Pulford K, Bernard F, Rousset T, Mason DY, Delsol G. Further demonstration of the diversity of chromosomal changes involving 2p23 in ALK-positive lymphoma: 2

- cases expressing ALK kinase fused to CLTCL (clathrin chain polypeptide-like). *Blood* 2000; **95**: 3204-3207 [PMID: 10807789 DOI: 10.1016/S0955-3886(00)00041-2]
- 5 **Zhang D**, Denley RC, Filippa DA, Teruya-Feldstein J. ALK-positive diffuse large B-cell lymphoma with the t(2;17)(p23;q23). *Appl Immunohistochem Mol Morphol* 2009; **17**: 172-177 [PMID: 19521280 DOI: 10.1097/PAI.0b013e31818629a8]
  - 6 **Parker BM**, Parker JV, Lymperopoulos A, Konda V. A case report: Pharmacology and resistance patterns of three generations of ALK inhibitors in metastatic inflammatory myofibroblastic sarcoma. *J Oncol Pharm Pract* 2019; **25**: 1226-1230 [PMID: 29925295 DOI: 10.1177/1078155218781944]
  - 7 **Cools J**, Wlodarska I, Somers R, Mentens N, Pedetour F, Maes B, De Wolf-Peeters C, Pauwels P, Hagemeijer A, Marynen P. Identification of novel fusion partners of ALK, the anaplastic lymphoma kinase, in anaplastic large-cell lymphoma and inflammatory myofibroblastic tumor. *Genes Chromosomes Cancer* 2002; **34**: 354-362 [PMID: 12112524 DOI: 10.1002/gcc.10033]
  - 8 **Wang WY**, Gu L, Liu WP, Li GD, Liu HJ, Ma ZG. ALK-positive extramedullary plasmacytoma with expression of the CLTC-ALK fusion transcript. *Pathol Res Pract* 2011; **207**: 587-591 [PMID: 21855232 DOI: 10.1016/j.prp.2011.07.001]
  - 9 **Le Deley MC**, Rosolen A, Williams DM, Horibe K, Wrobel G, Attarbaschi A, Zsiros J, Uyttebroeck A, Marky IM, Lamant L, Woessmann W, Pillon M, Hobson R, Mauguen A, Reiter A, Brugières L. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *J Clin Oncol* 2010; **28**: 3987-3993 [PMID: 20679620 DOI: 10.1200/jco.2010.28.5999]
  - 10 **Patte C**, Auperin A, Michon J, Behrendt H, Leverger G, Frappaz D, Lutz P, Coze C, Perel Y, Raphaël M, Terrier-Lacombe MJ; Société Française d'Oncologie Pédiatrique. The Société Française d'Oncologie Pédiatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. *Blood* 2001; **97**: 3370-3379 [PMID: 11369626 DOI: 10.1182/blood.v97.11.3370]
  - 11 **Armstrong F**, Duplantier MM, Trempat P, Hieblot C, Lamant L, Espinos E, Racaud-Sultan C, Allouche M, Campo E, Delsol G, Touriol C. Differential effects of X-ALK fusion proteins on proliferation, transformation, and invasion properties of NIH3T3 cells. *Oncogene* 2004; **23**: 6071-6082 [PMID: 15208656 DOI: 10.1038/sj.onc.1207813]
  - 12 **Brugières L**, Pacquement H, Le Deley MC, Leverger G, Lutz P, Paillard C, Baruchel A, Frappaz D, Nelken B, Lamant L, Patte C. Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: a report from the French Society of Pediatric Oncology. *J Clin Oncol* 2009; **27**: 5056-5061 [PMID: 19738127 DOI: 10.1200/jco.2008.20.1764]
  - 13 **Ruf S**, Hebart H, Hjalgrim LL, Kabickova E, Lang P, Steinbach D, Schwabe GC, Woessmann W. CNS progression during vinblastine or targeted therapies for high-risk relapsed ALK-positive anaplastic large cell lymphoma: A case series. *Pediatr Blood Cancer* 2018; **65**: e27003 [PMID: 29512859 DOI: 10.1002/pbc.27003]
  - 14 **Kodama T**, Hasegawa M, Takanashi K, Sakurai Y, Kondoh O, Sakamoto H. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. *Cancer Chemother Pharmacol* 2014; **74**: 1023-1028 [PMID: 25205428 DOI: 10.1007/s00280-014-2578-6]
  - 15 **Wrona A**. Management of CNS disease in ALK-positive non-small cell lung cancer: Is whole brain radiotherapy still needed? *Cancer Radiother* 2019; **23**: 432-438 [PMID: 31331844 DOI: 10.1016/j.canrad.2019.03.009]
  - 16 **Lin JJ**, Jiang GY, Joshipura N, Ackil J, Digumarthy SR, Rincon SP, Yeap BY, Gainor JF, Shaw AT. Efficacy of Alectinib in Patients with ALK-Positive NSCLC and Symptomatic or Large CNS Metastases. *J Thorac Oncol* 2019; **14**: 683-690 [PMID: 30529198 DOI: 10.1016/j.jtho.2018.12.002]
  - 17 **Gourd E**. Alectinib shows CNS efficacy in ALK-positive NSCLC. *Lancet Oncol* 2018; **19**: e520 [PMID: 30245054 DOI: 10.1016/s1470-2045(18)30707-1]
  - 18 **Tomlinson SB**, Sandwell S, Chuang ST, Johnson MD, Vates GE, Reagan PM. Central nervous system relapse of systemic ALK-rearranged anaplastic large cell lymphoma treated with alectinib. *Leuk Res* 2019; **83**: 106164 [PMID: 31226541 DOI: 10.1016/j.leukres.2019.05.014]
  - 19 **Reed DR**, Hall RD, Gentzler RD, Volodin L, Douvas MG, Portell CA. Treatment of Refractory ALK Rearranged Anaplastic Large Cell Lymphoma With Alectinib. *Clin Lymphoma Myeloma Leuk* 2019; **19**: e247-e250 [PMID: 30992232 DOI: 10.1016/j.clml.2019.03.001]
  - 20 **Verheijen RB**, Yu H, Schellens JHM, Beijnen JH, Steeghs N, Huitema ADR. Practical Recommendations for Therapeutic Drug Monitoring of Kinase Inhibitors in Oncology. *Clin Pharmacol Ther* 2017; **102**: 765-776 [PMID: 28699160 DOI: 10.1002/cpt.787]



Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-3991568  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

