Partial remission with sintilimab monotherapy in a patient carrying a *CD274* amplification in refractory diffuse large B-cell lymphoma: A case report

XIAN ZHANG[1*], LIYE XU[1*], EVENKI PAN[2], XIUHUA SUN[1] and XIAOLEI DING[1]

[1]Department of Medical Oncology, The Second Hospital of Dalian Medical University, Dalian, Liaoning 116023; [2]Department of Medical Services, Nanjing Geneseeq Technology Inc., Nanjing, Jiangsu 210031, P.R. China

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Abstract. Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease with varying characteristics, in terms of genomic variation, cell morphology and clinical presentation. At present, only ~66% of patients are cured with initial treatment and those with refractory DLBCL exhibit a poor prognosis. Thus, further investigations into novel effective treatment options for DLBCL are required. The present study reports the case of a patient resistant to multiple therapies, including rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) plus enzastaurin (trial no. CTR20171560), GemOx plus lenalidomide and selinexor (trial no. ATG-010-DLBCL-001). The patient harbored a *CD274* amplification, as identified via next-generation sequencing (NGS), and exhibited a high programmed death-ligand 1 Tumor Proportion Score of up to 95%. Consequently, the patient was treated with sintilimab monotherapy and the response lasted for 12 months of follow-up without major immune-related adverse events. This case highlights the role of NGS technology in selecting treatment options for refractory DLBCL. Furthermore, the results of the present study suggest that sintilimab may have potential in the treatment of patients with refractory DLBCL.

Correspondence to: Dr Xiuhua Sun or Dr Xiaolei Ding, Department of Medical Oncology, The Second Hospital of Dalian Medical University, 467 Zhongshan Road, Shahekou, Dalian, Liaoning 116023, P.R. China
E-mail: 3038668@vip.sina.com
E-mail: 510043951@qq.com

*Contributed equally

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), accounting for ~30% of all cases in Western Countries (1). DLBCL is a rapidly developing cancer that may metastasize to other areas of the body. Chemotherapy is the primary treatment for DLBCL, demonstrating efficacy in ~66% of patients and leading to a favorable prognosis (2,3). However, some patients may not respond to these treatments or may experience a relapse following initial treatment with standardized chemotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (3-5), leading to the development of relapsed/refractory DLBCL (r/r DLBCL). r/r DLBCL is a complex condition frequently associated with a poor prognosis (6,7). Although there are several treatment options available for patients with r/r DLBCL, such as R-CHOP, epigenetic therapy and targeted therapy, the therapeutic effects remain unsatisfactory (8).

Sintilimab is an immune checkpoint inhibitor (ICI) that blocks programmed cell death protein 1 (PD-1) on the surface of immune cells (9,10). PD-1 is a key checkpoint protein that prevents the immune system from targeting healthy cells. However, some tumor cells exploit this mechanism to evade immune surveillance. Sintilimab aids the immune system in identifying and attacking tumor cells by blocking PD-1 (9). Sintilimab has been approved in China for the treatment of multiple cancer types, including classical Hodgkin's lymphoma, advanced melanoma and non-small cell lung cancer (10), and is often administered in combination with other anticancer therapies (11,12). While sintilimab has demonstrated therapeutic efficacy against several types of advanced cancer, few studies have reported its use in the treatment of r/r DLBCL (13).

The present study describes the case of a patient with r/r DLBCL who experienced partial remission following treatment with four different regimens (R-CHOP, GemOx, selinexor and sintilimab). Based on the detection of *CD274* amplification via next-generation sequencing (NGS) and a high Tumor Proportion Score (TPS) for programmed death-ligand 1 (PD-L1) expression (95%) with the use of the commercially available PD-L1 IHC 22C3 pharmDx assay (Dako, Agilent Technologies, Inc.) (14), the patient was treated with sintilimab. The present case study emphasizes the importance of

NGS technology in choosing treatment options for DLBCL. It also proposes potential treatments for patients with refractory DLBCL.

Case report

In March 2019, a 60-year-old male patient presented to the Second Hospital of Dalian Medical University (Dalian, China) with epigastric pain, without fever, night sweats or weight loss. The patient had no history of abdominal disease. A computed tomography (CT)-guided biopsy was performed on lesions present in the hepatic hilar region. Subsequent pathological examination (Data S1) indicated NHL (Fig. 1A), which was specifically identified as DLBCL of non-germinal center origin (non-GCB). Immunohistochemical (IHC) analysis of the biopsy demonstrated the following results: CD3(-), Vimentin (partial +; Fig. 1B), CD5(-), CD10(-), BCL-6 (40% +; Fig. 1C), multiple myeloma 1 (80% +; Fig. 1D), BCL-2 (90% +; Fig. 1E), C-Myc (80% +; Fig. 1F), p53 (90% strong +; Fig. 1G), CD20 (diffuse strong +; Fig. 1H), CD30(-), CD21(-), Ki-67 (90% +; Fig. 1I) and PD-L1 (-; Fig. 1J). According to a positron emission tomography (PET)-CT scan, the tumor had metastasized to multiple areas of the body, such as the mediastinum, the hilar region of the liver, the superior and inferior borders of the posterior pancreas, the retroperitoneum, the left hilum of the liver, the left pelvic wall, the left parietal iliac vessels and lymph nodes, the spleen and both lungs (Fig. 2B and C). Thus, the patient was diagnosed with stage IV DLBCL (not otherwise specified, non-GCB) with an International Prognosis Index of 3 based on guidelines of Chinese Society of Clinical Oncology (CSCO) for lymphoid malignancies (Version 2019). The diagnosis and treatment timeline of the patient is shown in Fig. 2A.

According to the National Comprehensive Cancer Network guidelines (Version 4.2019), it is standard clinical practice for patients with stage IV DLBCL to participate in a clinical trial (15). Thus, the patient participated in a clinical trial (trial no. CTR20171560) in May 2019, and received an initial treatment of R-CHOP (rituximab 586 mg on d1, CTX 1.17 g on d2, ADM 78.2 mg on d2, VCR 2 mg on d2 and PDN 100 mg on d2-6 every 21 days) plus enzastaurin (500 mg every day). After three cycles of chemotherapy, stable disease was observed, and after six cycles of chemotherapy, a PET-CT scan indicated tumor shrinkage in the pancreas, peritoneum and retroperitoneum. However, the tumor in the left parietal iliac vessels increased from 1.3x0.8 to 2.0x1.1 cm, and the tumor in the spleen increased from 3.5x2.1 to 7.5x5.3 cm. In addition, the size of both pulmonary tumors had increased (Fig. 2B). Thus, the clinical response was evaluated as progressive disease in the case of r/r DLBCL. The subsequent treatment plan for the patient was based on the progress of the patient over time. In November 2019, the chemotherapy regimen was changed to GemOx (gemcitabine 1.6 g and oxaliplatin 150 mg on d1 every 14 days) plus lenalidomide (25 mg on d1-d14 every 21 days). After four cycles of this treatment, a partial response (PR) was achieved (Fig. 2B). At this time, the patient only underwent a chest CT to assess the treatment effectiveness and did not have a PET-CT in line with the preference of the patient. In August 2020, the disease progressed, with symptoms of abdominal pain, hoarseness, choking and a wet cough. Results of a subsequent PET-CT scan revealed a significant increase in the number and size of lesions, as well as an overall increase in metabolism and bone marrow involvement (Fig. 2C). Thereafter, the patient participated in another clinical trial (trial no. ATG-010-DLBCL-001) and was administered selinexor (ATG-010) (60 mg twice weekly with food). However, the response was not significant.

To explore new therapeutic treatments, a liver biopsy sample collected in March 2019 was further analyzed in September 2020, using NGS via the GeneseeqPrime® panel, which allowed for the targeted enrichment of 437 cancer-related genes (Supplementary methods). This NGS was performed by Nanjing Geneseeq Technology Inc. The results of the NGS revealed the presence of *MYD88* (c.794T>C, p.L265P) and *CD79B* (c.586T>C, p.Y196H) variants in the primary liver lesion (Table I), indicating that the patient had the *MYD88*/*CD79B*-mutated (MCD) subtype of DLBCL, which is associated with poor survival (2). A Bruton's tyrosine kinase (BTK) inhibitor was suggested as a treatment option; however, the patient declined due to financial concerns.

The condition of the patient deteriorated, with severe hoarseness, difficulty swallowing water and the presence of a neck swelling; thus, a biopsy was performed on the neck swelling. Pathological analysis confirmed the diagnosis of DLBCL. NGS analysis of the lymph node sample revealed amplifications of *CD274*, *PDCD1LG2* and *KRAS* (Fig. 3A). IHC confirmed the high expression levels of PD-L1 with TPS of 95%, which is encoded by *CD274* (Fig. 3B). NGS testing was also conducted on plasma samples simultaneously and it was found the *PPM1D Q571** mutation. This mutation was not detected in the lymph node sample, suggesting it may have originated from other lesions. The patient was therefore recommended immunotherapy with sintilimab (200 mg each day/21 days). The effects of sintilimab were assessed as PR after four cycles, and the response lasted for 12 months of follow-up. During the follow-up, the condition of the patient was partially improved. The treatment was well-tolerated with a slight decrease in leukocyte levels and no major immune-related adverse events (irAEs). The patient benefitted from sintilimab and there were no better treatment options available at that time, thus the patient continued with this treatment. During a telephone follow-up in November 2022, it was discovered that the patient had passed away. As no tests were conducted immediately before or after the death of the patient, the cause of death remains unknown.

Discussion

DLBCL is a type of cancer originating from B cells, a type of white blood cell that produces antibodies (16). DLBCL is the most frequent form of NHL in adults, accounting for ~30% of all cases in Western Countries (1). While the majority of patients with DLBCL respond well to chemotherapy, some may require alternative treatments.

In the present case, the patient was diagnosed with r/r DLBCL. The cell-of-origin typing indicated a non-GCB subtype and NGS further confirmed the MCD genotype, which is typically associated with a poor prognosis. The mutated MYD88 protein activates downstream NF-κB signaling pathways, which in turn promote tumor cell viability

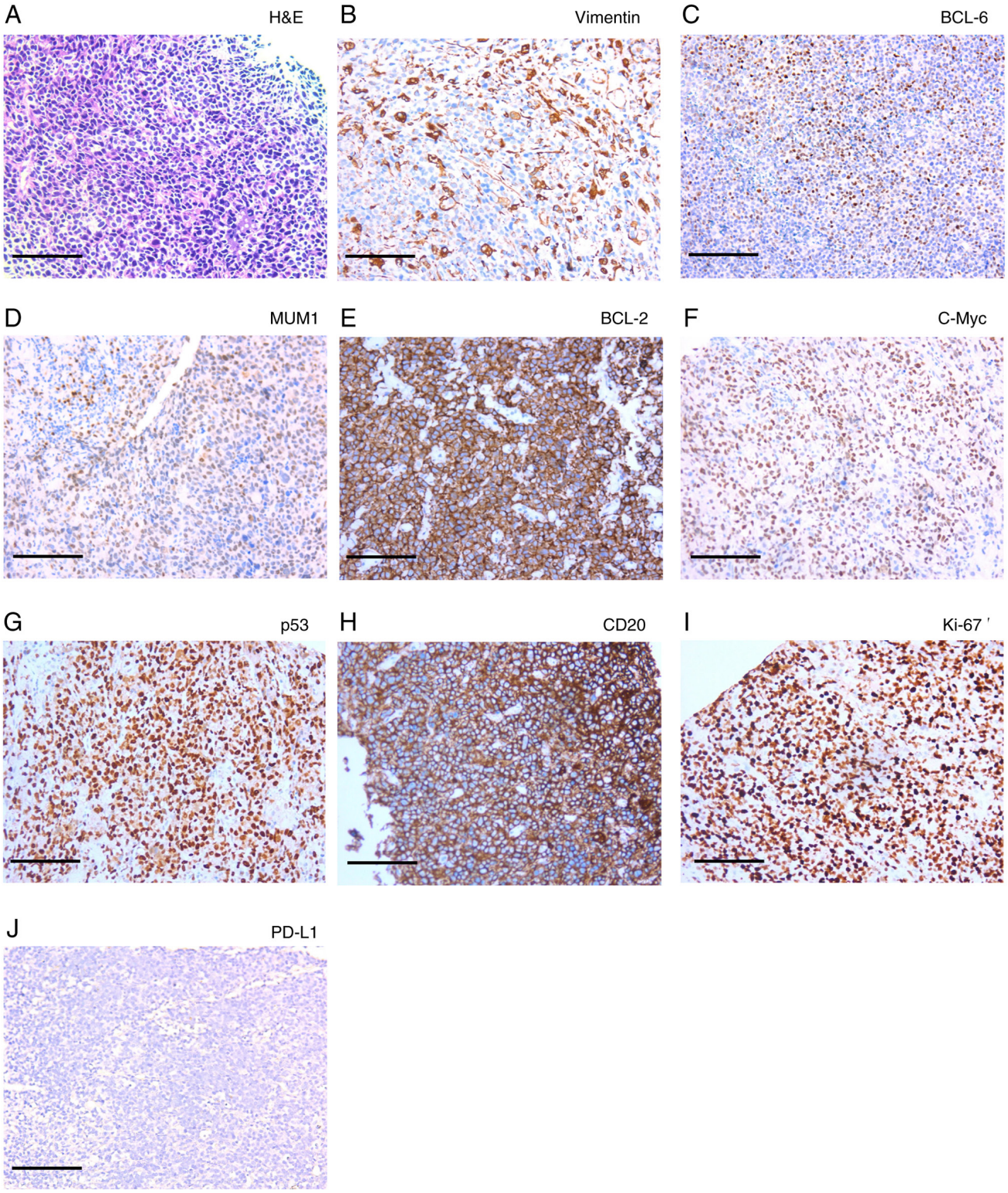

Figure 1. H&E and IHC staining of the lesions in the hepatic hilar region. (A) H&E staining of the hepatic hilar region (magnification, x200). IHC staining revealed that lesions in the hepatic hilar region were positive for (B) Vimentin (partial), (C) BCL-6 (40%), (D) MUM1 (80%), (E) BCL-2 (90%), (F) C-Myc (80%), (G) p53 (90%), (H) CD20 (diffuse strong) and (I) Ki-67 (90%), and (J) negative for PD-L1 (scale bar, 100 μm). IHC, immunohistochemical; MUM1, multiple myeloma 1; PD-L1, programmed death-ligand 1.

and proliferation (17). In early phase clinical trials, drugs such as BTK inhibitors, demonstrate efficacy against aberrant MYD88 signaling (18). However, the patient described in the present study was unable to access BTK inhibitors due to financial constraints.

After three lines of chemotherapy, the remaining treatment options for the patient remained limited. The patient was eventually treated with sintilimab based on the high PD-L1 expression levels and the NGS results indicating *CD274* amplification, and the response was satisfactory. Notably, *CD274*

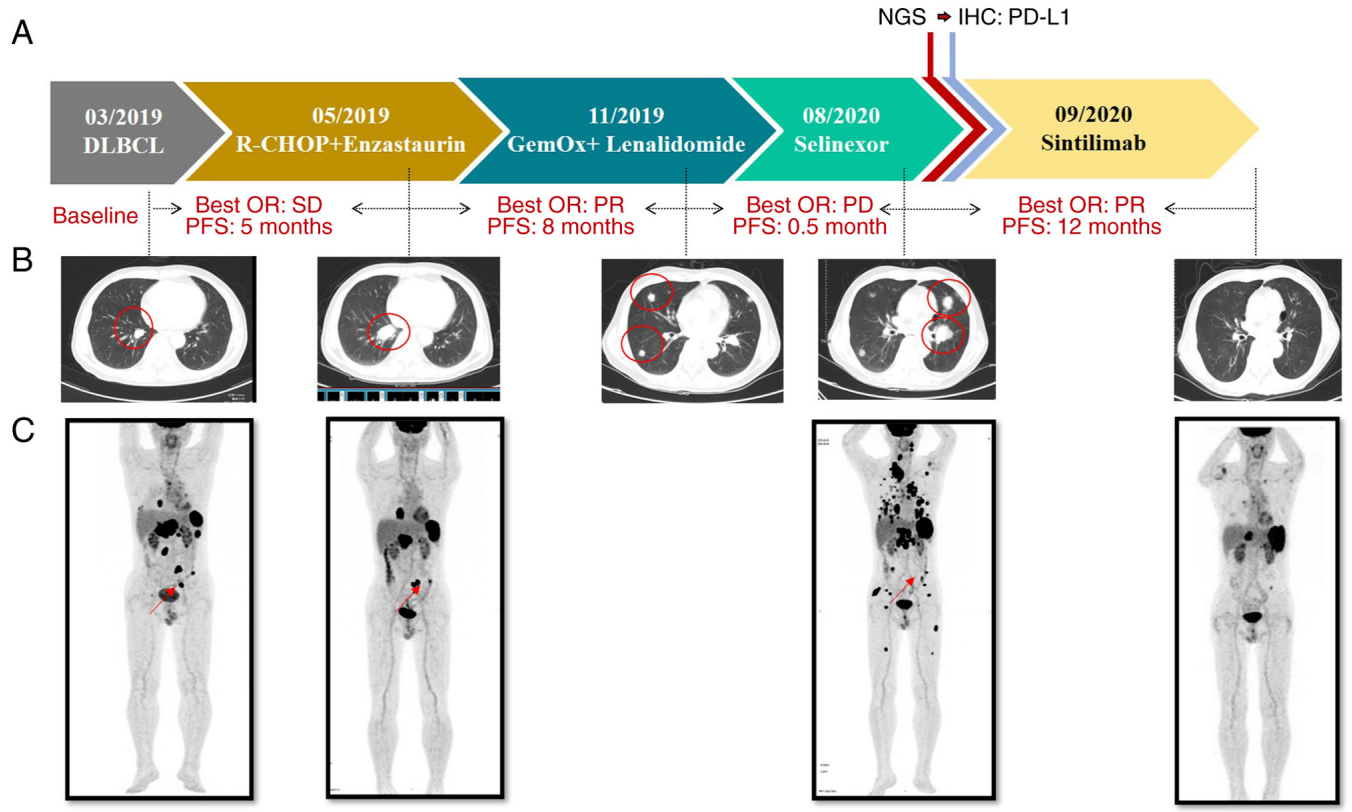

Figure 2. Treatment course and representative clinical images. (A) Disease timeline demonstrating the various treatment regimens administered to the patient and the corresponding clinical response. (B) Chest-CT and (C) positron emission tomography-CT scans demonstrating the disease progression following treatment. CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; IHC, immunohistochemical; NGS, next-generation sequencing; OR, objective response; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease.

amplification and PD-L1 expression were not detected in the liver lesion upon initial diagnosis; however, these factors were observed in the cervical lymph node metastases following progression after multiple therapies. These results may be indicative of a resistance mechanism.

Despite being a relatively uncommon variation in DLBCL, *CD274* amplification may impact disease progression and clinical response. *CD274* amplification is associated with an upregulation of PD-L1, a protein that controls the activity of immune cells through binding to PD-1 receptors (Fig. 3C). Upregulation of PD-L1 in DLBCL promotes tumor growth by inhibiting the immune response against cancer cells. The results of previous studies have demonstrated that genomic level variations that cause PD-L1 upregulation include gene rearrangements involving the 9p24.1 gene locus, which contains the *CD274* (PD-L1), *PDCD1LG2* (PD-L2) and *JAK2* genes, or 9p24.1 copy gains and amplifications (19,20). Other variations, such as *SP140* and *PD-L1* translocation, *PD-L1* and *PD-L2* inversion, and translocations between *PD-L1* and *IGH*, *PIM1* or *TP63* (19), may also contribute to PD-L1 upregulation. These alterations were shown to be greatly enriched in the activated B cell-like/non-GCB subtype and were highly associated with high PD-L1 protein expression levels (21). Furthermore, patients with these molecular features demonstrated notable therapeutic responses to PD-1 inhibitors (22). In addition to PD-L1 expression, previous studies have also investigated the effects of the immune microenvironment and tumor-infiltrating lymphocytes on anti-PD-1 immunotherapies, and the results demonstrated that both the PD-1/PD-L1 and CD73/A2aR signaling pathways promoted an immunosuppressive microenvironment in DLBCL, affecting patient response to PD-1 inhibitors (23).

In the present study, the patient responded well to sintilimab monotherapy, in terms of tumor response and prognosis. However, not all patients respond to such treatment, and some may experience serious side effects, such as irAEs. Official guidelines of instructions for sintilimab injection (2020) state that the adverse effects of sintilimab are pneumonia, diarrhea, colitis, hepatitis, nephritis, endocrinology diseases, skin AEs, infusion reactions and other irAEs (24). If patients experience severe adverse reactions, sintilimab treatment should be stopped, and suitable symptomatic treatment may be administered. The results of previous studies demonstrated that anti-PD-1 drugs, either administered as a monotherapy or in combination regimens, exhibit limited efficacy in the treatment of patients with r/r DLBCL (25-28). In a phase I clinical trial, nivolumab exhibited antitumor activity in 11 patients with r/r DLBCL, with an objective response rate (ORR) of 36% (25). In a phase II clinical trial, nivolumab was used in the treatment of 121 patients with DLBCL, and the ORR was <10%. In the same trial, in cohorts with and without autologous hematopoietic cell transplantation, the median progression-free survival (PFS) time was 1.9 and 1.4 months, respectively, and the median overall survival (OS) time was 12.2 and 5.8 months, respectively (26). A total of 38 patients with r/r DLBCL were included in the

Table I. Genetic alterations detected by targeted next-generation sequencing of the right cervical lymph node and liver metastasis lesions, and the plasma sample.

Gene	Mutation	Genotype	Plasma, %	FFPE: Lymph node, %	FFPE: Liver metastasis
CD79B	p.Y196H	c.586T>C	-	38.5	49.2%
MYD88	p.L265P	c.794T>C	-	56.1	58.4%
CD274	Amplification	-	-	-	CN: 106.4
PDCD1LG2	Amplification	-	-	-	CN: 77.3
KRAS	Amplification	-	-	-	CN: 4.1
TP53	p.R175H	c.524G>A	-	86.0	63.5%
TP53	p.V216M	c.646G>A	-	-	24.6%
BRCA1	p.K339Rfs*2	c.1016del	-	-	17.9%
MYC	Fusion:IGH~MYC	IGH~MYC: exon2	-	22.9	1.5%
PPM1D	p.Q571*	c.1711C>T	1.8	-	-
PRDM1	p.K235*	c.703A>T	-	54.2	47.6%
AKT1	p.R370H	c.1109G>A	-	-	14.8%
ASXL3	p.P1765S	c.5293C>T	-	44.4	47.6%
BCL2	p.A43_148delinsRM	c.127_144delinsCGCATG	-	-	13.7%
BRIP1	p.Q634H	c.1902G>C	-	-	22.0%
BTG2	p.A155T	c.463G>A	-	46.8	51.8%
BTG2	p.H52Y	c.154C>T	-	28.6	30.2%
CD274	p.1258M	c.774C>G	-	15.1	14.8%
CHEK2	p.G159E	c.476G>A	3.1	-	-
CIITA	p.1255F	C.763A>T	5.1	-	-
DICER1	p.L987V	c.2959C>G	1.2	-	-
DTX1	p.V26_H34delinsY	c.76_100delinsT	-	8.2	22.5%
EP300	p.P157A	c.469C>G	-	13.9	21.6%
ETS1	p.D6N	c.16G>A	-	51.3	52.0%
ETV6	p.K11N	c.33G>C	-	70.7	74.2%
FAS	P.D108G	c.323A>G	-	53.3	64.6%
H1-4	p.G70D	c.209G>A	-	47.6	40.8%
INPP5D	p.S27T	c.80G>C	-	41.7	27.0%
LYST	p.M1647T	c.4940T>C	-	30.4	27.3%
MSH6	p.H1351Y	c.4051C>T	-	25.9	-
MYC	p.S388R	c.1164C>G	-	29.1	-
NFKBIA	p.A133T	c.397G>A	-	35.3	21.7%
PIM1	p.E226K	c.676G>A	-	60.7	46.4%
PIM1	p.S45R	c.135C>A	-	28.0	19.8%
PIM1	p.P124S	c.370C>T	-	15.1	20.1%
PIM1	p.K274_L275del	c.821_826del	-	11.7	-
PIM1	c.345 355+8del	c.345 355+8del	-	-	15.0%
PIM1	c.513+1_513+19delinsCTGAGGAGT	c.513+1_513+19delinsCTGAGGAGT	-	-	14.7%
ROS1	p.P1756S	c.5266C>T	-	-	31.7%
STIL	p.N1056S	c.3167A>G	-	-	12.6%
TBL1XR1	p.A416P	c.1246G>C	-	35.3	20.8%

FFPE, formalin-fixed, paraffin-embedded; CN, copy number; -, not detected.

KEYNOTE-155 study, and the results demonstrated an ORR of 21.1% following treatment with pembrolizumab plus the CDK9 inhibitor, dinaciclib. In addition, the median PFS and OS times were 2.1 and 7.9 months, respectively (27). A total of 32 patients with r/r DLBCL were included in another phase II clinical trial, and the results demonstrated an ORR of 33% following treatment with lenalidomide in combination with rituximab. In addition, the median PFS

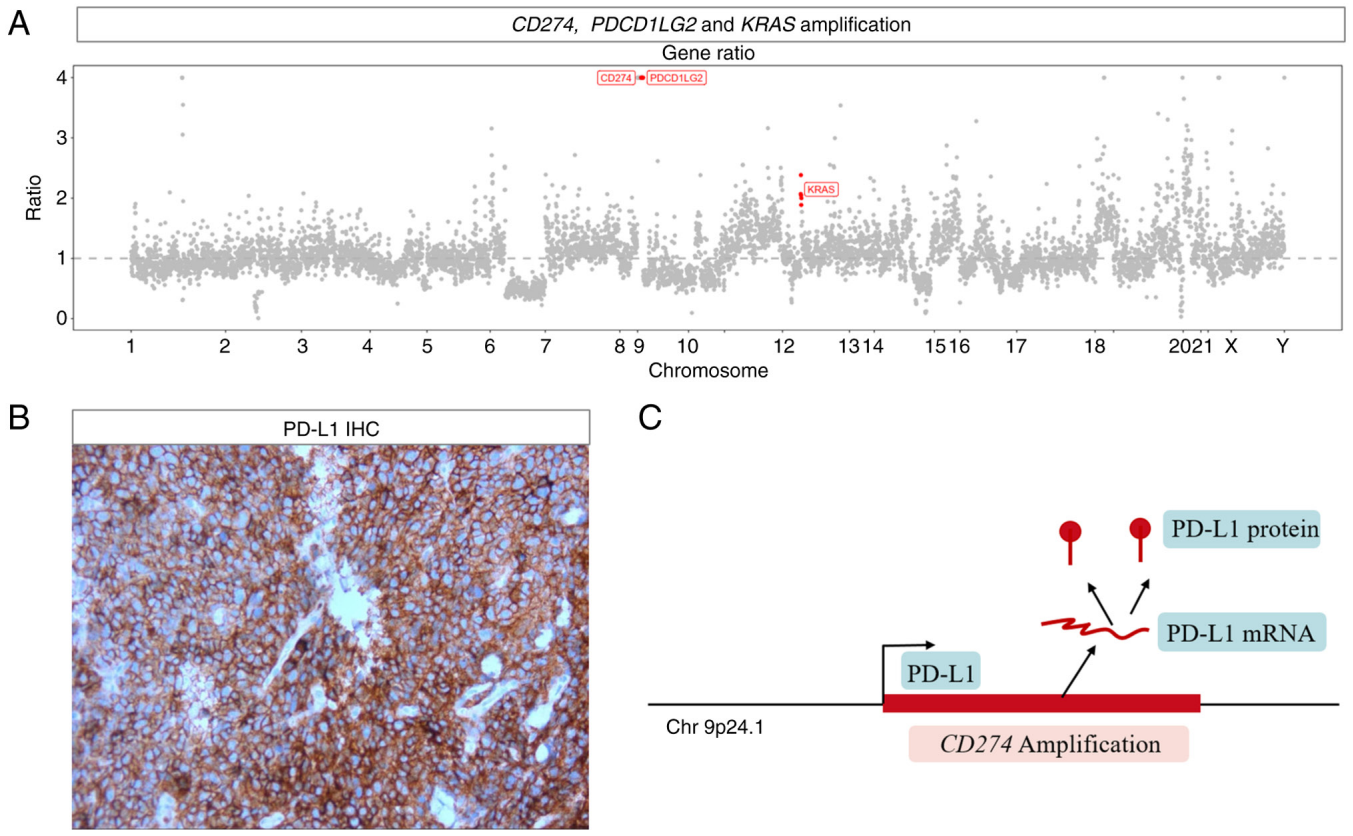

Figure 3. Genomic variations of the patient. (A) *CD274*, *PDCD1LG2* and *KRAS* amplification detected via next-generation sequencing. (B) IHC examination of PD-L1 (magnification, x200; scale bar, 100 μm). (C) *CD274* gene amplification modulates PD-L1 gene expression. IHC, immunohistochemical; PD-L1, programmed death-ligand 1.

and OS times were 3.7 and 10.7 months, respectively (28). However, further clinical trials are required to investigate the effectiveness and potential side effects of ICIs in the treatment of DLBCL. In addition, the results of a previous case report suggested that the combined use of sintilimab and chidamide may have potential in the treatment of patients with r/r DLBCL, resulting in a prolonged complete remission. However, during the combination therapy, the patient experienced adverse events due to chidamide, including thrombocytopenia and neutropenia (13). Thus, it is necessary for patients to undergo long-term follow-up, to determine the durability of the partial remission achieved with sintilimab monotherapy or combination therapy.

PD-L2 (encoded by *PDCD1LG2*) is a protein that regulates the immune response through binding to the PD-1 receptor on T cells (29). While high levels of PD-L2 expression have been associated with improved responses to immunotherapy in certain cancer types, including non-small cell lung cancer and melanoma (30), the role of PD-L2 expression in DLBCL is yet to be fully elucidated. Although *KRAS* mutations are not commonly observed in patients with DLBCL, these mutations may be associated with aggressive disease development and poor clinical outcomes (31). Thus, the identification of *KRAS* mutations in patients will aid in determining appropriate treatment strategies, as these patients may require more intense or innovative therapies to overcome drug resistance or immune evasion mediated by abnormal KRAS proteins.

NGS is a powerful tool that provides valuable insights into the genome of an individual (32). NGS aids in identifying genomic variations that may be associated with specific diseases or conditions, promoting earlier diagnoses and the selection of more effective treatment options (33,34). Furthermore, blood-based liquid biopsies have the potential to facilitate the early detection of cancer, thereby improving the chances of patient recovery (35). In the present case, NGS was instrumental in the molecular diagnosis of the patient and provided guidance for the potential use of sintilimab in patients with r/r DLBCL. Following the use of conventional treatment modalities for DLBCL, NGS may provide insight into potential treatment alternatives. In addition, the results of a previous study revealed that the analysis of metabolites may assist in revealing the real-time status of biological systems. For example, metabolomics showed potential in the early diagnosis, treatment and prognosis prediction of patients with breast cancer, demonstrating an additional tool for early screening and diagnosis (36).

The present study exhibited several limitations. For example, a single patient was included in the present study, meaning that additional experiments were limited. Further investigations that examine the effects of the immune microenvironment or tumor-infiltrating lymphocytes are required. Further prospective studies are also required to confirm the efficacy of sintilimab in patients with r/r DLBCL. In addition, the efficacy of sintilimab monotherapy remains to be fully elucidated. Thus, further investigations

that explore the potential of sintilimab in combination with other targeted therapies or immunotherapies are required.

In conclusion, DLBCL is a complex disease with numerous different subtypes and potential genomic variations. Understanding the specific molecular mechanisms of DLBCL has contributed to the development of targeted therapies and immunotherapies that may improve the survival of patients with this disease. However, additional investigations are required to further the current understanding of the disease and determine novel therapeutic options.

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Availability of data and materials

The sequencing results and raw data generated in the present study may be found in the BioProject database under accession numbers PRJNA1066705 and PRJNA1086347 or at the following URLs: https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1066705 and https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1086347.

Authors' contributions

XZ designed this study and collected the data for this case report. LX conceived the present study. EP analyzed and interpreted of data. XS acquired the data. XD made substantial contributions to conception and design. XS and XD confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The clinical trials in which the patient participated were approved by the Ethics Committee of The Second Hospital of Dalian Medical University (Dalian, China), including R-CHOP plus enzastaurin (trial no. CTR20171560) and selinexor (trial no. ATG-010-DLBCL-001).

Patient consent for publication

Written informed consent to publish the clinical details and images were obtained from the patient's relative.

Competing interests

EP is employed by Nanjing Geneseeq Technology, Inc. Nanjing Geneseeq Technology, Inc. is a tumor gene testing company, and the present study may help to promote the application of NGS technology, enhance the company's reputation and drive the company's business. The remaining authors declare that they have no competing interests.

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