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Case Report

Clinicopathological features and treatment of aggressive natural killer cell leukemia: case series and literature review

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ABSTRACT

Background. Aggressive natural killer cell leukemia (ANKL) is rare and difficult to diagnose in early stages, with no standard treatment and a poor prognosis.

Case presentation. Two adolescents with ANKL presented with hemophagocytic lymphohistiocytosis (HLH), with Case-1 presenting as refractory HLH and Case-2 with lung involvement. The morphology of bone marrow showed an increase in unidentified cells, which mainly expressed CD56. Cytogenetic analysis showed complex karyotypes. Both patients received intensive combined chemotherapy based on pegaspargase and anthracyclines. Case-1 died of tumor lysis syndrome. Case-2 underwent hematopoietic stem cell transplantation and is currently alive and disease-free.

Conclusions. HLH can serve as the initial manifestation of ANKL. Leukemia cells of ANKL have significant variations in the morphology and mainly express CD56. Intensive combination chemotherapy based on pegaspargase and anthracyclines may be considered for ANKL.

Key words: aggressive NK cell leukemia, asparaginase, anthracyclines, hemophagocytic lymphohistiocytosis.

Aggressive natural killer cell leukemia (ANKL) is a rare systemic mature natural killer (NK) cell proliferating tumor with an aggressive and fulminant clinical course.[1,2] It usually presents with fever, systemic symptoms, leukemic hemogram, and elevated serum lactate dehydrogenase levels and may be accompanied by hemophagocytic lymphohistiocytosis (HLH), disseminated intravascular coagulation (DIC), or multiple organ failure.[1,2] The commonly involved sites include bone marrow, peripheral blood, lymph nodes, liver, and the spleen, while the involvement of skin, soft tissue, lung, and omentum is rare.[2] ANKL occurs mainly in adults between 30 and 50 years of age, and there are only occasional reports of cases in children.[1,2]

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The early diagnosis of ANKL is difficult mainly due to the complexity of clinicopathological manifestations (mimicking many syndromes or diseases) and the lack of specific immunophenotype and molecular biological characteristics.[3,4] At present, the conventional treatment is chemotherapy based on L-asparaginase (L-ASP) and allogeneic hematopoietic stem cell transplantation (allo-HSCT).[1,2] However, the complete remission (CR) rate of chemotherapy is below 36%.[5-7] The 1-year cumulative incidences of relapse or progression has been found to be 55.5% after allo-HSCT.[7] The prognosis is poor, and the median survival time is less than 2 months.[1,2,6,8]

Herein, we report the diagnosis and treatment of two cases of ANKL manifested as HLH in children, of which one case with lung involvement has survived for 19 months after allo-HSCT.

Case Presentations

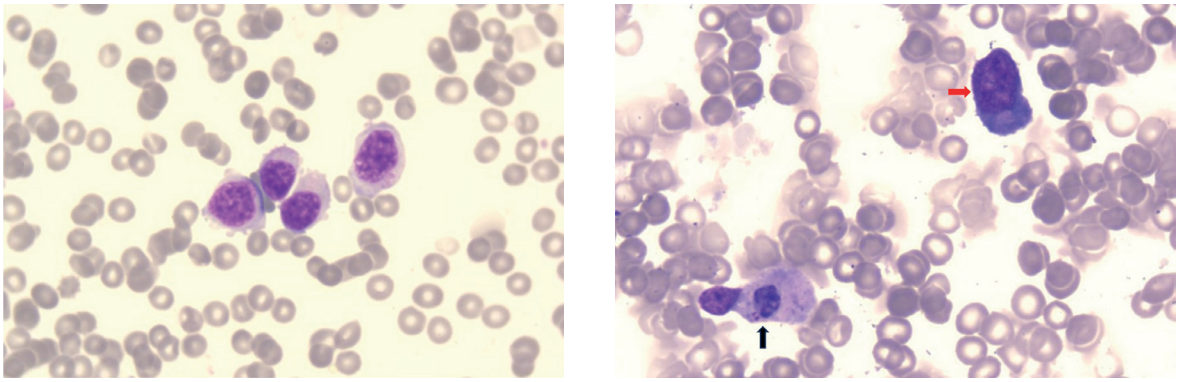
Case-1

A 15-year-old female patient was admitted to our hospital for recurrent fever of three months. Before admission, Epstein-Barr virus (EBV) infection-associated HLH was diagnosed due to recurrent fever, splenomegaly, pancytopenia, elevated triglycerides (4.69 mmol/L, range: 0-1.7 mmol/L), elevated ferritin (7,876 ng/mL, range: 30-400 ng/mL), hemophagocytosis in the bone marrow, elevated soluble CD25 (20,881.06 pg/mL, range: 410-2,623 pg/mL), and EBV-DNA 3.17×10^4 copies/mL (range: ≤ 5.0×10^3 copies/mL). The tests of NK cell activity and cerebrospinal fluid were normal. The detection of mutations in primary HLH-related genes was negative. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT) showed splenomegaly with diffuse metabolic elevation (maximum standardized uptake value [SUVmax]: 3.5). The treatment response was partial remission after five weeks of chemotherapy of the HLH-2004 protocol (dexamethasone, etoposide, and cyclosporine). Subsequently, she received two cycles of the COP regimen (cyclophosphamide, vindesine, and prednisone) and two cycles of the L-DEP regimen (pegaspargase, adriamycin, etoposide, and methylprednisolone). However, she still had recurrent fever, splenomegaly, and ferritin levels exceeding 3500 ng/mL during chemotherapy. Empirical anti-infection treatments including meropenem, linezolid, and voriconazole did not improve the recurrent fever.

After admission, physical examination revealed anemia, skin ecchymosis, and splenomegaly. Peripheral blood cell counts showed leucocyte count 1.52 × 10^9/L, neutrophil count 1.41 × 10^9/L, hemoglobin concentration 62 g/L, and platelet count 51 × 10^9/L. Laboratory tests showed ferritin 58,250 ng/mL, triglycerides 4.4 mmol/L, decreased NK cell activity (0.57%, range: ≥ 15.11%), soluble CD25 4,846.49 pg/mL, hemophagocytosis in the bone marrow, and EBV-DNA 5.74×10^3 copies/mL. C-reactive protein, procalcitonin, and erythrocyte sedimentation rates were 75.54 mg/L (range: <5 mg/L), 0.23 ng/mL (range: <0.05 ng/mL), and 103.0 mm/h (range: ≤15 mm/h), respectively. The tests of tubercle bacillus, 1,3-β-D-glucan, and galactomannan were negative. No evidence of rheumatic immune diseases and malignancies was found. Re-induction therapy with HLH-2004 protocol was given. Meanwhile, empirical anti-infection treatments including meropenem, linezolid, and voriconazole were given. However, the patient still experienced recurrent fever, pancytopenia, splenomegaly, ferritin levels > 45,000 ng/mL, and triglyceride levels > 5.5 mmol/L during the re-induction treatment. Bone marrow aspiration was performed again after four weeks of re-induction therapy, and bone marrow smear showed 80% of unidentified cells (Fig. 1A). Immunophenotype of abnormal cells by flow cytometry was CD56+, CD2+, CD94+, CD30+, CD38+, CD3-, CD4-, CD8-, CD5-, CD7-, $TCR_{\alpha\beta}$-, $TCR_{\gamma\delta}$-, CD16-, CD10-, CD25-, CD57-, and CD161-. The diagnosis of ANKL was given. VDLP (vincristine, idarubicin, pegaspargase, and prednisone) regimen was adopted for induction chemotherapy. During the induction chemotherapy, she experienced tumor lysis syndrome and finally died of multiple organ failure.

Case-2

A 14-year-old male patient was admitted to our hospital due to fever with a dry cough for two weeks and chest pain for three days. Physical examination revealed anemia, hepatomegaly, and splenomegaly. Peripheral blood cell counts showed leucocyte count 0.83 × 10^9/L, neutrophil count 0.38 × 10^9/L, hemoglobin concentration 93 g/L, and platelet count 43 × 10^9/L. Laboratory tests showed fibrinogen 1.35 g/L (range: 2-4 g/L), triglycerides 4.12 mmol/L (range: 0.3-1.92), ferritin 25,297 ng/mL, NK cell activity 15.68% (range: ≥ 15.11%), soluble CD25 34,957 pg/mL, and EBV-DNA 2.2×10^5 copies/mL. C-reactive protein, procalcitonin, and erythrocyte sedimentation rates were 32.04 mg/L, 0.45 ng/mL, and 8 mm/h, respectively. The tests



A. B.

Fig. 1. The morphology of bone marrow. **A.** Abnormal cells in the bone marrow smear of Case-1 (Wright Giemsa stain, ×1,000). The abnormal cells were irregular in shape and large in size, with granules in the cytoplasm, some of which had pseudopodia. **B.** Abnormal cells and hemophagocytosis (the black arrow) in the bone marrow smear of Case-2 (Wright Giemsa stain, ×1,000). The abnormal cells (the red arrow) had a large size, abundant basophilic cytoplasm, and fine nuclear chromatin.

of 1,3-β-D-glucan, galactomannan, tubercle bacillus, and bacterial culture (blood) were negative. The bone marrow smear showed 22.5% of unidentified cells and hemophagocytosis (Fig. 1B). Immunophenotype of abnormal cells by flow cytometry was CD45++, CD56++, CD2+, CD94+, CD33+, HLA-DR+, CD81+, CD16-, CD117-, CD34-, CD13-, CD10-, CD19-, CD11b-, CD7-, CD5-, CD36-, CD64-, CD4-, CD8-, sCD3-, cyMPO-, cyCD79a-, cyCD3-, and CD123-. High resolution computed tomography of the chest showed multiple space-occupying lesions in both lungs. The manifestations of 18F-FDG-PET/CT images (Fig. 2) were as follows: (1) There were multiple soft tissue density masses and nodules in both lungs, with the largest located in the anterior segment of the superior lobe of the right lung (the maximum cross-section of approximately 44 × 50mm), lobulation at the edge, low-density necrosis at some centers, and increased radioactive uptake (SUVmax: 11.8). (2) Bones of the whole body showed uneven increased radioactive uptake (SUVmax: 11.3), but computed tomography showed no bone destruction. Serum tumor markers such as carcinoembryonic antigen, carbohydrate antigen 72-4, neuron specific enolase, squamous cell carcinoma antigen, and pro-gastrin-releasing peptide were all negative. The pathology of the lung mass puncture biopsy showed a large area of coagulative necrosis, the peripheral residual small focal fibrous tissue presented as chronic inflammation with collagenization and fibrous exudation, and the severe tissue necrosis. The diagnosis of HLH and ANKL was given. The detection of mutations in primary HLH-related genes was negative. The treatment response was partial remission after three weeks of chemotherapy of HLH-2004 protocol (dexamethasone, etoposide). However, there was no improvement in pulmonary space-occupying lesions. Subsequently, for ANKL, the patient underwent allo-HSCT, after chemotherapy with EDCH+P regimen (vincristine, cyclophosphamide, dexamethasone, liposome doxorubicin, etoposide, and pegaspargase; two cycles), DDGP regimen (cisplatin, dexamethasone, gemcitabine, and pegaspargase), and chidamide combined with etoposide and dexamethasone regimen. Currently, the patient is alive and disease-free.

Discussion

The diagnosis of ANKL in children meets numerous challenges. First, the clinical manifestations are diverse and mimic a variety of syndromes and diseases, making early diagnosis difficult.[3,4] Second, the morphology

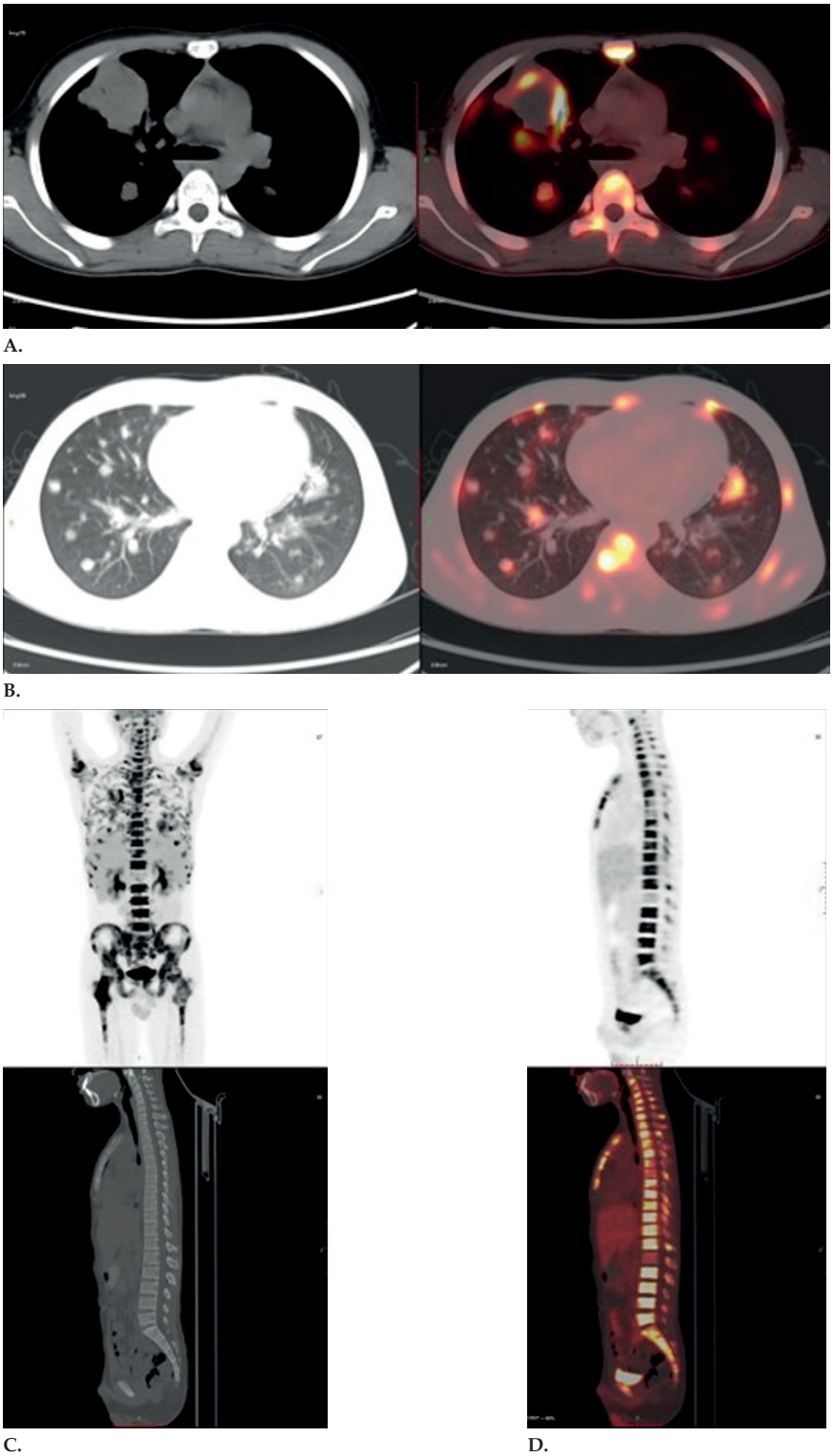


Fig. 2. The manifestations of 18F-FDG-PET/CT of Case-2. **A.** and **B.** Masses and nodules in lungs, with increased radioactive uptake (SUVmax: 11.8). **C.** and **D.** Bones of the whole body, with uneven increased radioactive uptake (SUVmax: 11.3), but no bone destruction in the computed tomography.

of leukemic cells of ANKL are significantly different.[9,10] Third, abnormal NK cells in ANKL mainly expressed CD56, but with no specific immunophenotype, and CD56-negative cases accounted for 16.7%.[11,12] Fourth, cytogenetics show complex karyotypes without any specificity.[13,14] Finally, no specific fusion gene or mutant gene may be found.

Therefore, we systematically analyzed the clinical and pathological manifestations, bone marrow morphology, immunophenotyping, cytogenetic and molecular biology characteristics, and treatment of 19 children with ANKL (including our two cases and 17 cases[3,8,15-29] from China Biology Medicine disc and Pubmed) in this study. General clinical characteristics of these 19 cases are summarized in Table I.

ANKL had a variety of clinical manifestations. The median age was 14 years (range: 0.75–18 years), and adolescent patients accounted for 63.2%. Most patients presented with fever (89.5%), splenomegaly (89.5%), hepatomegaly (57.9%), and anemia (68.4%). Leukopenia, thrombocytopenia, and elevated serum lactate dehydrogenase level were identified in 61.1% (11/18), 68.4% (13/19), and 100% (12/12) of the patients, respectively. Nine patients (56.3%) were positive for EBV. Six patients (31.6%) developed HLH, of which two patients initially presented with relapsed/refractory HLH. DIC occurred in five patients (26.3%), three of which had experienced it before chemotherapy. Three patients had medullary masses. Detailed data can be found in Supplementary Table I.

The morphological, immunophenotypic, cytogenetic, and molecular biological characteristics of bone marrow in 19 children with ANKL are summarized as follows. First, the morphology of bone marrow was mainly characterized by the increase in the number of unidentified cells or large granular lymphocytes. The abnormal cells were irregular in shape, medium or large in size, and medium to rich in basophilic cytoplasm containing azurophil granules. The cytoplasm of some cells had vacuolization, pseudopodium-like apophyses, or tails. The shape of the nucleus was irregular, the karyoplasmic ratio was large, the chromatin was diffuse, and the nucleolus was visible. Second, abnormal cells mainly expressed CD56 (100%) and CD2 (76.9%), partially expressed CD7 (45.5%) and CD16 (40.0%). No abnormal cell population was detected by flow cytometry in two patients (10.5%), but the immunohistochemistry of solid tissues (testes or bone marrow) showed that CD56 was positive. Third, the cytogenetic analysis showed that ANKL mainly manifested complex karyotype (63.6%), but specific chromosomal abnormalities were lacking. Finally, no specific fusion genes or mutant genes were found. Detailed data can be found in Supplementary Tables II and III.

Ten out of the 19 children with ANKL underwent intensive combined chemotherapy based on L-ASP and/or anthracyclines. CR occurred in four patients (40%) and partial remission (PR) in two patients (20%). Two patients received allo-HSCT and achieved disease-free survival. Tumor lysis syndrome occurred in 10.5% of patients during the course of treatment. Four patients (21.1%) were lost at follow-up, and nine patients (60%) died. Detailed data can be found in Supplementary Table IV.

Thus, combining the condition and diagnostic process of our two patients, the diagnosis of ANKL mainly relies on the morphology and immunophenotype of bone marrow. When the diagnosis of ANKL is difficult, the following measures help confirm the diagnosis: (1) The pathology and immunohistochemistry of bone marrow or extramedullary mass biopsy[30], because the immunophenotype of abnormal NK cells in different sample types (bone marrow, peripheral blood, and lymph nodes) is consistent.[14] (2) For CD56-negative patients, CD94 and CD335 help in identifying NK cell tumors because both of them are highly expressed in NK cell tumors.[31,32]

Table I. General clinical characteristics of 19 enrolled ANKL patients.

Characteristics	No. of patients available	No. of abnormal patients (%)
Age, years		
Median (range): 14 (0.75-18)	19	
≥13		12 (63.2)[3,15,16,20-22,24,25,27,28]
<13		7 (36.8)[8,17-19,23,26,29]
Sex	19	
Male		14 (73.7)[3,8,16,18-21,23-26,28,29]
Female		5 (26.3)[15,17,22,27]
Country	19	
Asia		15 (78.9)[15-21,24-29]
Non-Asia		4 (21.1)[3,8,22,23]
Clinical manifestation		
Fever	19	17 (89.5)[3,8,16-24,26-29]
Anemia	19	13 (68.4)[8,16-20,22,25-27,29]
Hemorrhage	19	5 (26.3)[17,18,21,29]
Hepatomegaly	19	11 (57.9)[3,8,17,19,20,23,24,26-28]
Splenomegaly	19	17 (89.5)[3,8,16-19,21-29]
Lymphadenopathy	19	5 (26.3)[15,19,20,24,27]
Extramedullary mass	19	3 (15.8)[15,26]
Skin lesion	19	1 (5.3)[19]
Hyperleukocytosis (leukocyte count > 100×10^9/L)	19	1 (5.3)[8]
Leukopenia (leukocyte count < 4×10^9/L)	18	11 (61.1)[15-17,22,23,25,27-29]
Thrombocytopenia	19	13 (68.4)[3,16-18,22-25,27-29]
Elevated serum lactate dehydrogenase level	12	12 (100)[3,15-20,22,27,29]
Epstein-Barr virus positive	16	9 (56.3)[8,15,17,20,22,23,28]
Disseminated intravascular coagulation	19	5 (26.3)[3,17,21,24]
Hemophagocytic lymphohistiocytosis	19	6 (31.6)[3,17,23,28]
Central nervous system leukemia (newly diagnosed patients)	19	0 (0)
Bone marrow examination		
Morphology	19	17 (89.5)
Unidentified cells	17	11 (64.7)[8,15,16,19,20,23,26,27,29]
Large granular lymphocytes	17	4 (23.5)[17,18,22,28]
Immunophenotype	19	18 (94.7)
CD56	18	18 (100)[3,8,15-20,22-29]
CD2	13	10 (76.9)[3,17-20,22-24]
CD7	11	5 (45.5)[3,16,17,20,24]
CD16	10	4 (40)[3,20,22,24]
cCD3	11	3 (27.3)[23-25]
CD8	10	2 (20)[23,28]

ANKL, aggressive natural killer cell leukemia.

Table I. Continued.

Characteristics	No. of patients available	No. of abnormal patients (%)
Cytogenetics	19	11 (57.9)
Complex karyotype	11	7 (63.6)[17,22-24,27]
Common abnormal chromosomes		
Chromosome 8	11	4 (36.4)[17,22,26]
Chromosome 21	11	4 (36.4)[17,27]
Chromosome 7	11	3 (27.3)[17,23]
Molecular biology	19	5 (26.3)
Specific fusion gene	5	0 (0)
Specific mutant gene	5	0 (0)
Treatment	19	18 (94.7)
Chemotherapy based on L-asparaginase and/or anthracyclines	18	10 (55.6)[8,15,16,24-28]
Complete remission	10	4 (40)[24,25,27,28]
Partial remission	10	2 (20)[8]
Relapse	10	1 (10)[26]
Hematopoietic stem cell transplantation	18	2 (11.1)[28]
Tumor lysis syndrome	18	2 (11.1)[8]
Prognosis	19	15 (78.9)
Loss at follow-up	19	4 (21.1)[15,20,21,26]
Deaths	15	9 (60)[3,16-19,22,23,29]

ANKL, aggressive natural killer cell leukemia.

Combining the treatment of our two patients and the literature review mentioned above, the intensive combination chemotherapy based on L-ASP and anthracyclines may be considered for the initial treatment of ANKL to achieve a better response. A multicenter retrospective study in adults showed that 3 of 13 patients receiving chemotherapy based on anthracycline/anthraquinone achieved CR, compared with none of the 8 patients who received chemotherapy without anthracycline.[33] Meanwhile, the overall survival (OS) rate of patients receiving L-ASP-based combined chemotherapy significantly improved[6] because L-ASP was not affected by P-glycoprotein (encoded by *MDR1*, a multidrug resistance gene) highly expressed by NK cell tumor cells. In addition, the AIEOP-95 high-risk acute lymphoblastic leukemia (ALL) regimen[25] and ALL-BFM95 regimen[27], both based on L-ASP and anthracyclines, resulted in long-term disease-free survival.

In conclusion, HLH can serve as the initial manifestation of ANKL. The diagnosis of ANKL is challenging and depends mainly on the morphology and immunophenotype of bone marrow. Intensive combination chemotherapy based on asparaginase and anthracycline may be considered for ANKL.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2024.5072

Ethical approval

The study was approved by Medical Ethics Committee of Affiliated Hospital of Qingdao University (date: 28.07.2021, number: QYFY WZLL 26613 and date: 11.07.2023, number: QYFY WZLL 27941). Informed consent of our two cases was obtained from their parents.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: YN, LS, LL, YW; data collection: LL, YW; analysis and interpretation of results: YN, LS; draft manuscript preparation: YN. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declares that there is no conflict of interest.

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