



Acute myeloid leukemia arising to genetic susceptibility genes related T cell acute lymphoblastic leukemia: case report

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Abstract: Fanconi anemia (FA) is the most common inherited bone marrow failure disorder, with a predisposition to neoplasia. While Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are the most common hematologic malignancies seen in patients with FA, cases of acute lymphoblastic leukemia (ALL) have also been described in the literature but it is uncommon. In our case report, a 12 years 5 months old boy, who was detected with heterozygote mutation of *FANCC* gene and nonsynonymous single nucleotide variability (SNV) mutation of *AKAP9* gene, presented with precursor T cell ALL (T-ALL) at onset, myelodysplasia or myeloid biomarkers were not found at initial diagnosis. He received chemotherapy and achieved complete remission (CR) after a course of remission induction, but severe cytopenia was presented, sepsis and Invasive fungal infection also arose. With following-up and continue chemotherapy, secondary AML arose 17 months later, the patient died of sepsis related to chemotherapy at AML status. FA patients usually presented with homozygous or bilateral heterozygosity mutation in literature reports, whereas heterozygosity gene mutation of *FANCC* and *AKAP9* has not reported yet. AKAP9 protein which was encoded by *AKAP9* gene is widely distributed in many kinds of cells, thus ensuring the specificity and accuracy of signal transduction. We speculate that AKAP9 protein may interfere with the normal signal transduction of heterozygous mutation expression of *FANCC* gene and result in the inactivation of *FANCC* gene function. Unfortunately, the patient died of sepsis and we don't have enough blood samples to explore the role of *AKAP9* gene mutation in patients with heterozygosity *FANCC* gene mutation.

Keywords: Fanconi anemia (FA); acute myeloid leukemia (AML); acute lymphoblastic leukemia (ALL); children; case report

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Introduction

Fanconi anemia (FA), autosomal recessive or X-linked disease, is heterogeneous phenotype. Associated with abnormal response to DNA damage, FA is characterized by congenital abnormally, progressive bone marrow failure, and predisposition to neoplasm (1). There was 16% of FA patients developed hematologic malignancies and 10% of them developed solid tumors (2). While Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are the most common hematologic malignancies seen in

patients with FA, cases of acute lymphoblastic leukemia (ALL) have also been described in the literature (3). Homozygous or compound heterozygous mutations are usually detected in patients with FA (1), hence we reported a rare case with FA who presented with precursor T cell ALL (T-ALL) at onset, secondary AML arose after he received chemotherapy and got complete remission (CR), however inherited heterozygote mutation of *FANCC* and heterozygous nonsynonymous single nucleotide variability (SNV) mutation of *AKAP9* were confirmed.

We present the following case in accordance with the

CARE reporting checklist (available at <http://dx.doi.org/10.21037/acr-20-151>).

Case presentation

A 12 years 5 months old boy was admitted with fever, pale, hepatosplenomegaly, lymphadenectasis and pancytopenia. He had no growth retardation, past history and family history of tumor or cytopenia were also not mentioned. Initial complete blood count (CBC) showed as: white blood cell (WBC) count $1.7 \times 10^9/L$, red blood cell (RBC) count $2.83 \times 10^{12}/L$, hemoglobin (Hgb) 84 g/L, platelet (PLT) count $62 \times 10^9/L$, blast cell was not detected in peripheral blood smear. FAB subtype, which was checked by bone marrow (BM) smear (*Figure 1A,B*) and biopsy (*Figure 1C,D,E,F,G*), was ALL, evidence of myelodysplasia were not found; immunophenotype of T-ALL was confirmed by immunohistochemical staining (*Figure 1A*) and flow cytometry, positive myeloid biomarkers were undetectable (FCM, *Figure 1H*); chromosome karyotype is normal (46,XY[20]); fluorescence *in situ* hybridization (FISH) of *ETV6/RUNX1*, *TCF3/PBX1*, *BCR/ABL* and *MLL* rearrangement (*MLLr*) were negative; common fusion genes were screened by multiplex nest reverse transcriptase polymerase chain reaction (multiplex nested RT-PCR) as literature report (4) and results were also negative. Radiographs of the whole skeleton were normal. The patient received chemotherapy according to modified St. Jude Total XV protocol for newly diagnosed pediatric ALL (5). He achieved CR after a course of induction remission, but severe cytopenia (Lowest value of WBC or absolute neutrophils count was $0.34 \times 10^9/L$ or $0.02 \times 10^9/L$) was presented, sepsis and invasive fungal infection arose. He was classified as intermediate risk (IR) group by minimal residual disease (MRD) monitoring as protocol request, chemotherapy was followed by a course of consolidation, continuous and maintenance therapy (5).

Seventeen months later (in course of maintenance therapy), the patient was again presented with fever, pallor, osteodynia and hepatosplenomegaly. CBC showed as: WBC $27.39 \times 10^9/L$ with 85% blast cell, RBC $1.88 \times 10^{12}/L$, Hgb 61 g/L, PLT $73 \times 10^9/L$. FAB subtype was classified as AML with myelodysplasia by BM smear (*Figure 2A,B,C,D*) and biopsy (*Figure 2E,F,G*), AML was also confirmed by FCM (*Figure 2H*); chromosome karyotype was normal; FISH of *RUNX1/ETO*, *CBFb*, *PML/RARa*, *BCR/ABL* and *MLLr* and fusion genes screen as literature (4) were negative.

BM sample of the patient in ALL status, which was

preserved in liquid nitrogen, and in AML status, peripheral blood samples of his elder sister and parents were collected, whole exome sequencing (WES) was detected for these samples by next generation sequencing (NGS), detectable pathologic gene mutations were checked by Sanger sequencing (6). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The parents of the patient provided written informed consent to publish the case report and accompanying images.

Somatic pathologic mutations of *WT1*, *DNM2*, *GATA* and *JAK3* were found in the AML status and ALL status samples. Heterozygous nonsense mutation of *FANCC* (NM_001243744:exon7:c.C553T: p.R185X) and heterozygous nonsynonymous mutation of *AKAP9* (NM_147185:exon23:c.G5705A: p. R1902H) were detected in the sample of the patient under both ALL and AML status; heterozygous mutation of *FANCC* and *AKAP9* was detected in his father and mother respectively, while heterozygous mutation of *FANCC* was also detected in his elder sister (*Figure 3*). Peripheral blood lymphocytes of the patient in 1st CR status which was preserved in liquid nitrogen were collected, mitomycin C (MMC) induced chromosomal breakage tests were done as literature reports for the family (7,8), positive results was found in the patient (*Figure 4*) and negative results were detected in his parents and sister.

Accumulate dosage of DNR was 210 mg/m^2 in preceding treatment for ALL, therefore the patient received chemotherapy consisted of etoposide (VP-16 $100 \text{ mg/m}^2/\text{d}$, day1–3) and cytarabine (AraC $200 \text{ mg/m}^2/\text{d}$, day1–7). Severe side effects, including significant myelosuppression and severe infection, were presented; the patient died of sepsis and invasive fungal infection three weeks after chemotherapy.

Discussion

FA is divided into several subgroups according to its genetic mutations (1). Sixteen known mutated genes that are associated with FA had been reported, most of such subgroups are autosomal recessive diseases, of which *FANCB* mutation is X-linked disease (9). Patients with FA are characterized by hypersensitivity to DNA cross-linking or alkylating agents, such as ultra-violet radiation and MMC, that block DNA replication and RNA transcription,

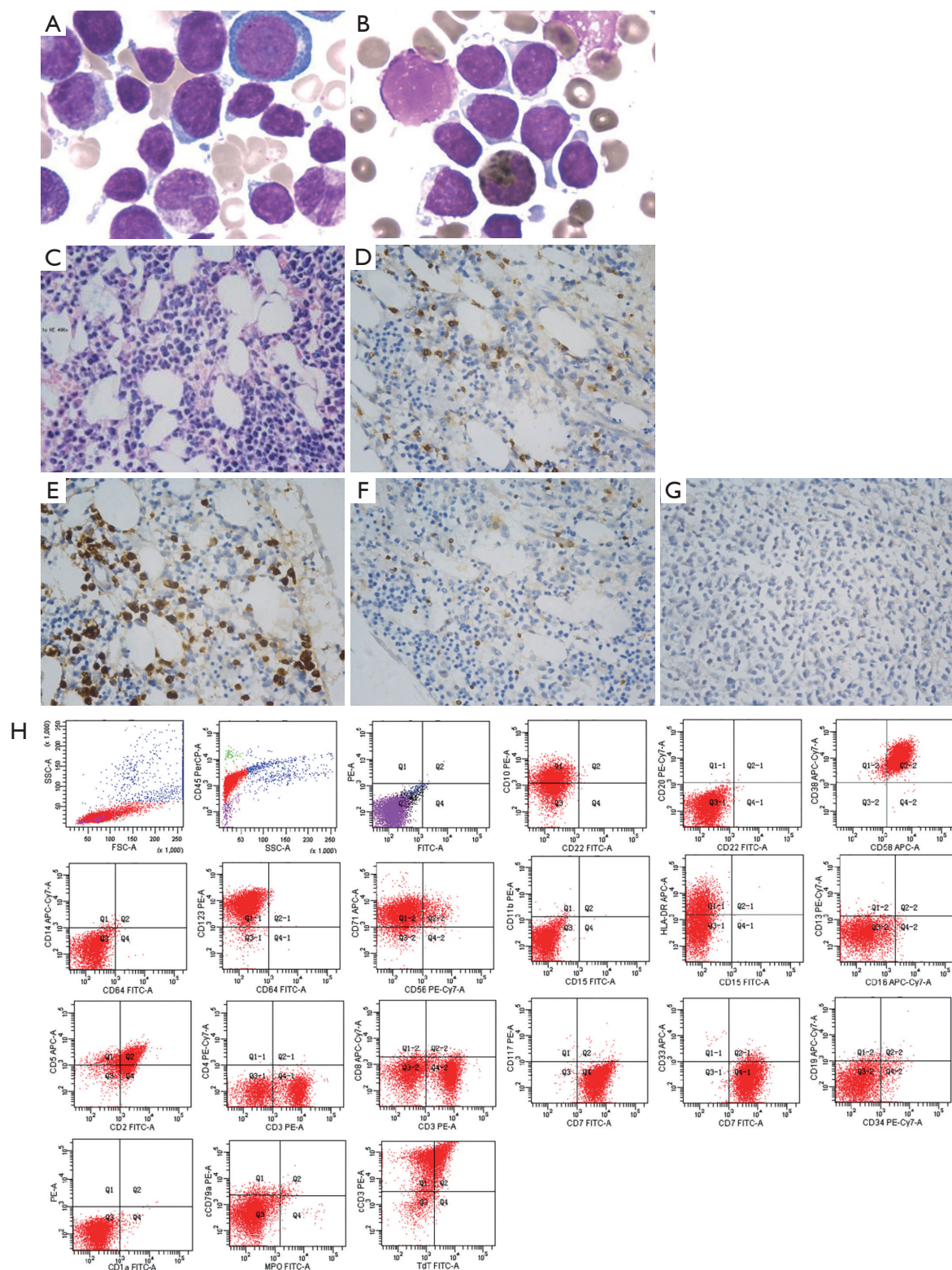


Figure 1 BM for the patient in ALL status. (A) BM smear by Wright's stain (100×). (B) BM smear by histochemical stain (POX-, 100×). (C) BM biopsy by HE stain (400×). (D) BM biopsy by IHC stain (CD7-, 400×). (E) BM biopsy by IHC stain (MPO-, 400×). (F) BM biopsy by IHC stain (PAX-5+, 400×). (G) BM biopsy by IHC stain (CD2-, 400×). (H) BM by FCM.

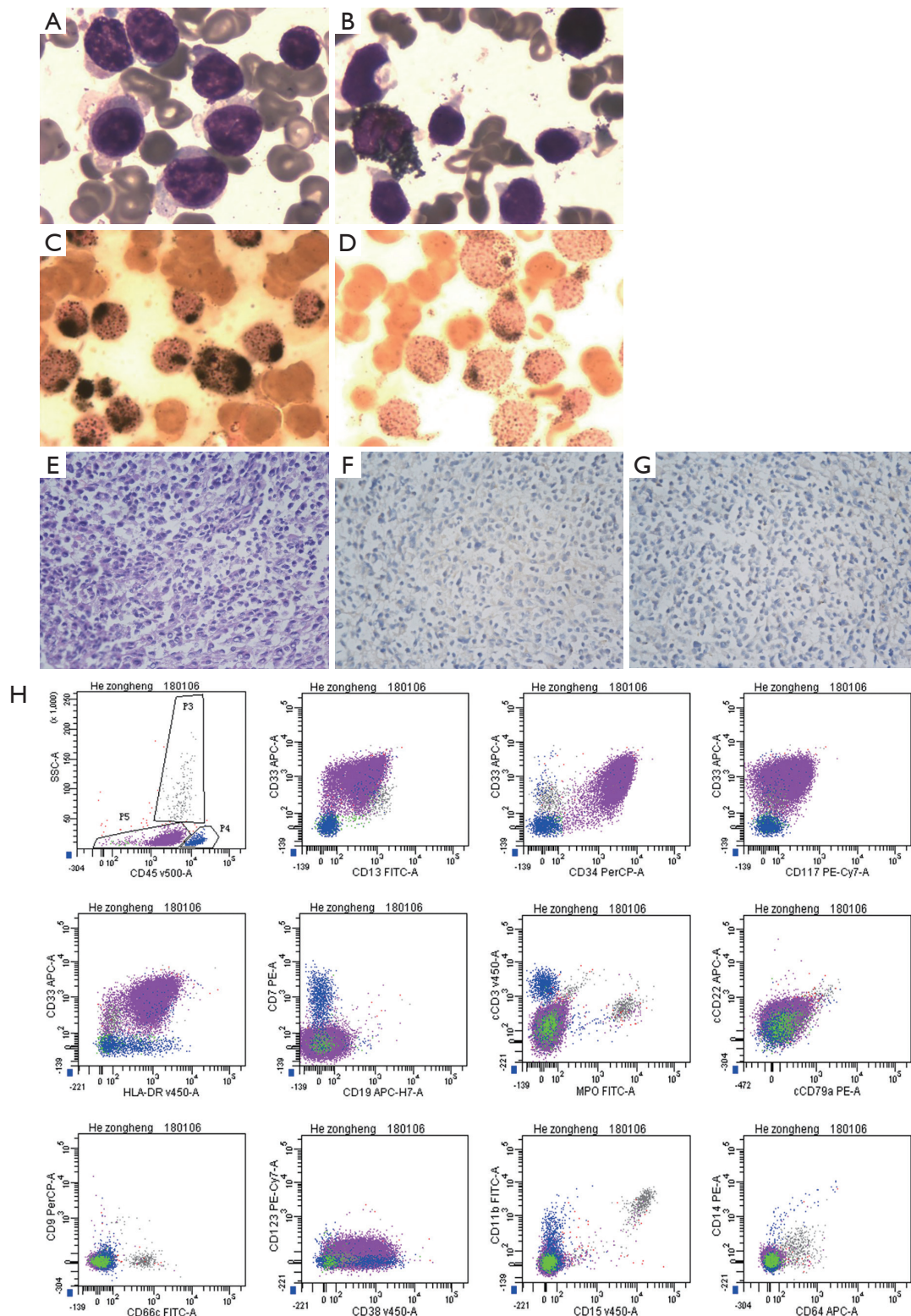


Figure 2 BM for the patient in AML status. (A) BM smear by Wright's stain (100×). (B) BM smear by histochemical stain (POX+, 100×). (C) BM smear by histochemical stain (NAE+++), 100×). (D) BM smear by histochemical stain (NAE-NaF+, 100×). (E) BM biopsy by HE stain (400×). (F) BM biopsy by IHC stain (CD3-, 400×). (G) BM biopsy by IHC stain (CD7-, 400×). (H) BM by FCM.

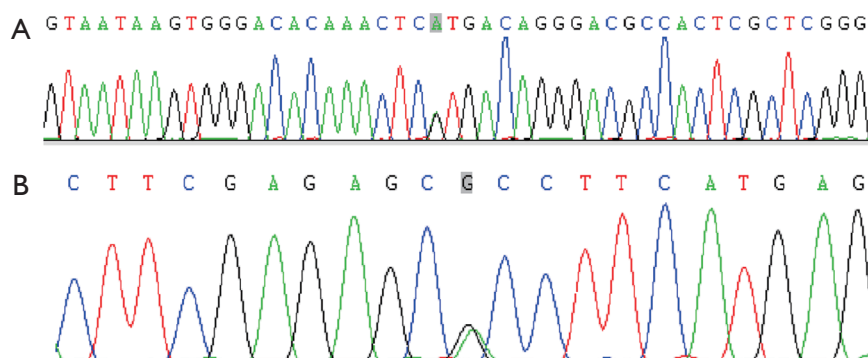


Figure 3 Sanger sequencing of gene mutation. (A) *FANCC* gene mutation: G/A. (B) *AKAP9* gene mutation: G/A.



Figure 4 Chromosomal breakage test (×100).

chromosomal breakage test and comet assay test play important role in the diagnosis of FA (8,9). Homozygous or bilateral heterozygote mutations are usually detected in FA patients (1), however heterozygote mutation of *FANCC* and heterozygous nonsynonymous SNV mutation of *AKAP9* were confirmed in the reported patient; clinical diagnosis of FA was considered because of positive results for chromosomal breakage test and comet assay test.

Associated with abnormal response to DNA damage, FA patients have a very high risk of congenital malformation, bone marrow failure and malignancies (2). Although FA is well-known for its relationship to hematologic malignancies, literature reviews had suggested that FA patients are highly predisposed to solid tumors (1). A review of 1301 FA patients who were diagnosed from 1927 to 2001 had reported 192 (14.76%) cases of leukemia/MDS and 105 (8.07%) cases of solid tumor (3); 754 FA patients were enrolled in a 20-year prospective study on the

International Fanconi Anemia Registry, 601 cases (79.71%) suffered from bone marrow failure, 173 cases (22.94%) suffered from neoplasms which included 120 cases of hematologic malignancies and 79 cases of non-hematologic neoplasm respectively (2). The most common subgroup of hematologic malignancies in FA patients is AML/MDS of which incidence is approximately 15%, whereas ALL, in which most of them were T-ALL, is rare (10,11).

In literature reports (1,8,9), FA patients presented with homozygous or bilateral heterozygosity mutation, whereas heterozygosity mutation of *FANCC* and *AKAP9* has not reported in FA patients. The A-kinase anchor proteins (*AKAPs*) are a group of structurally diverse proteins, which have the common function of binding to the regulatory subunit of protein kinase A (PKA) and confining the holoenzyme to discrete locations within the cell (11). There are at least 50 members, often named after their molecular mass, and *AKAP9* protein is encoded by *AKAP9* gene which is located in 7q21.2. *AKAPs* are widely distributed in many kinds of cells. Different signal transduction enzymes are recruited near the substrate. Thus, upstream activators and downstream factors are effectively assembled into a macromolecular signal transduction complex, which integrates various signal molecules that co-regulate the phosphorylation of cell substrates, thus ensuring the specificity and accuracy of signal transduction (12). We speculate that *AKAP9* protein may interfere with the normal signal transduction of heterozygous mutation expression of *FANCC* gene and result in inactivation of *FANCC* gene function. Unfortunately, the patient died of sepsis and we don't have enough blood samples to explore the role of *AKAP9* mutation in patients with heterozygosity *FANCC* mutation.

Conclusions

In brief, ALL in patients with FA is rarely reported, we present a FA patient who was lack of classic FA manifestation and FA family history, he was onset with T-ALL and secondary AML with myelodysplasia was developed after he achieved CR. Literature reports about ALL related to FA patients are limited and most of such patients were T-ALL. Primary diagnosis of FA usually is ignored when patients presented with ALL, WES should be detected when the secondary tumor arose; further studies are needed to determine for the appropriate chemotherapy regimen in these patients.

Most FA patients were detected with homozygous or bilateral heterozygote mutation, the reported patients were detected heterozygote mutation of *FANCC* and heterozygous nonsynonymous SNV mutation of *AKAP9*, we suspected that *AKAP9* gene and its protein affect *FANCC* gene by interfering with signal transduction, which leads to the occurrence and development of leukemia, further research is needed to confirm it.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/acr-20-151>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/acr-20-151>). The authors have no conflicts of interest to declare.

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. Ethical approval for the publication of this case was obtained from the

ethical committee of Children Hospital of Chongqing Medical University. All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). The parents of the patient provided written informed consent to publish the case report and accompanying images.

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