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Severe congenital neutropenia and liver abscess: Surgical treatment breaks the vicious cycle

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ABSTRACT

Here, we present a case with genetically confirmed SCN. The main symptom of the child was recurring fever. The combination of antibiotics combined with G-CSF injection was proved to be insufficient, and the patient developed "solid" liver abscess. After undergoing surgical anatomical hepatic lobectomy, the child's infection symptoms showed improvement. The postoperative culture of the purulent material from the liver infection lesion revealed an infection with Staphylococcus aureus. Our case raises the possibility of pathogen sources and routes of infection, clinical characteristics, and effective treatment for SCN patients with concomitant liver abscess.

1. Introduction

Severe congenital neutropenia (SCN) is a rare primary immunodeficiency disorder associated with hematopoietic dysfunction, characterized by impaired differentiation and severely reduced absolute numbers of neutrophils due to arrested bone marrow maturation [1]. As a result, the children with SCN often experience persistent or recurrent fever and infections in the first year of life [2]. Liver abscess is one of the rare and highly dangerous infectious complications in SCN patients [3]. The persistence of infected foci not only increases the risk of distant infectious shock, organic lesions and drug resistance, but also predisposes the patient to G-CSF treatment dependence, which in turn increases the susceptibility to hematologic diseases such as leukemia and myelodysplastic syndrome (MDS). There are currently few reports and no standard guidelines for the optimal treatment of SCN in children with concurrent liver abscesses. Herein, we present a genetically confirmed case of an SCN patient who had poor response to combined anti-infective therapy with G-CSF due to recurrent fever. During treatment, the patient developed liver abscesses and underwent surgical resection of the affected lobe, which was found to be infected by Staphylococcus aureus based on postoperative pathology results. At one-month follow-up after surgery, the patient responded well to the hepatic lobectomy and showed no recurrence of symptoms such as fever or diarrhea.

Abbreviations: SCN, severe congenital neutropenia; MDS, myelodysplastic syndrome; ANC, absolute neutrophil count; ACMG, American College of Medical Genetics and Genomics; NE, neutrophil elastase.

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Table 1
Blood smear test.

date	segmented neutrocyte	lymphocyte	monocytes	Eosinophilic granulocyte	Basophilic granulocyte	Neutrophil granulocyte
4.10	NA	0.88	0.11	0.01	NA	rare
4.11	0.04	0.6	0.29	0.06	0.01	rare
4.14	0.02	0.53	0.33	0.09	NA	rare

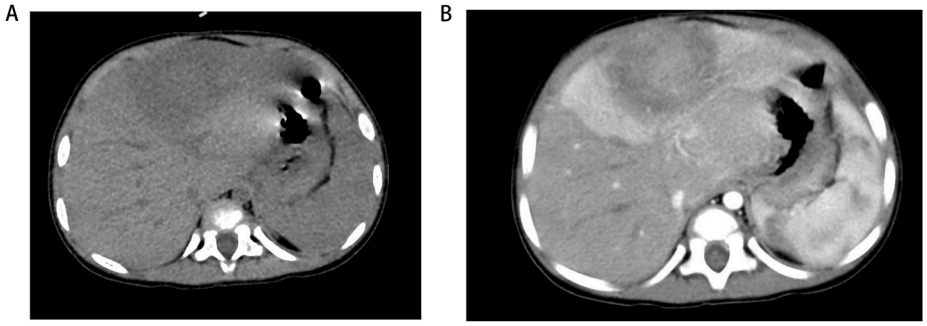


Fig. 1. Plain and enhanced CT scan of upper abdomen: (A) There was a patchy, slightly low-density shadow in segment IV of the liver. The inner density was uneven, with blurred edges, and the size was about 52mm × 36mm × 48mm (left and right × front and rear × up and down). **(B)** There was abnormal perfusion of liver parenchyma around the lesion in arterial phase. The lesions in delayed phase showed honeycomb enhancement, and the size of the lesion in enhanced area was smaller than that of the plain scan, suggesting that the surrounding area was edema. The lesions showed a certain mass effect, and the left hepatic vein and left portal vein were not clearly visualized.

2. Case description

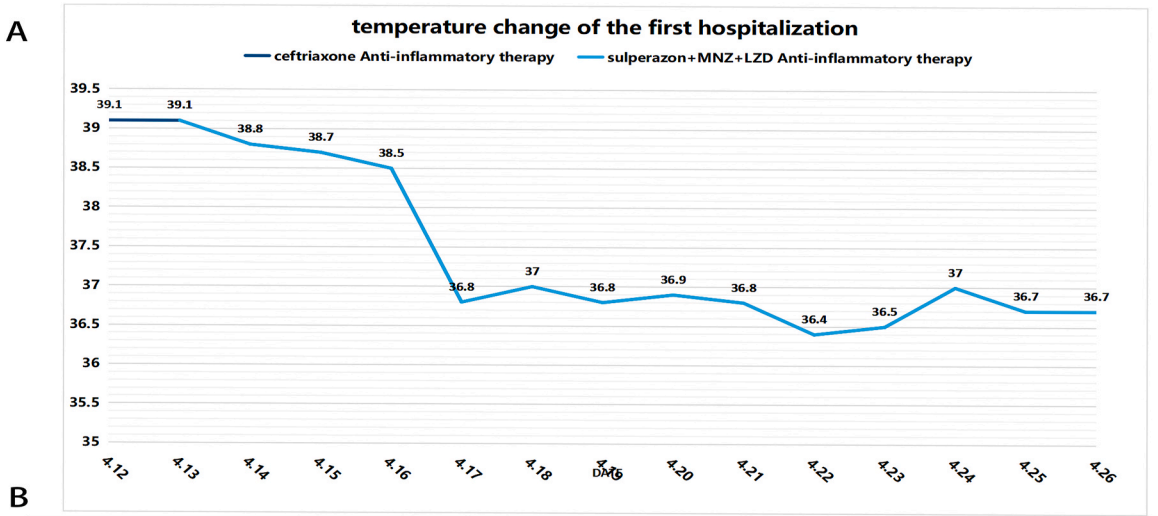
An 11-month-old male child born to non-consanguineous parents developed fever one week after receiving the measles vaccine. The child's family treated him with "Cefuroxime Axetil Granules" medication, and his temperature dropped to normal within 2–3 days but could not be maintained, and the condition recurred for about 10 days. After three months, the child was admitted to the respiratory department due to an increase in fever frequency and a decrease in fever relief time to 8–12 hours. Physical examination on admission showed congestion of the pharynx, grade 1 swelling of both tonsils, coarse breath sounds in both lungs, and no other positive signs were found. Laboratory auxiliary tests showed a significant increase in inflammatory markers: white blood cells were $20.2\hat{}10^9$/L, CRP was 146.4mg/L, procalcitonin was 0.69ng/mL, and ESR was 120mm/h. Blood film examination revealed rare neutrophils (Table 1). Imaging examination of abdominal CT suggests a possible deep organ infection with an associated mass effect(Fig. 1B): hepatic abscess, measuring approximately 5.3x3.4x3.9cm(Fig. 1A).

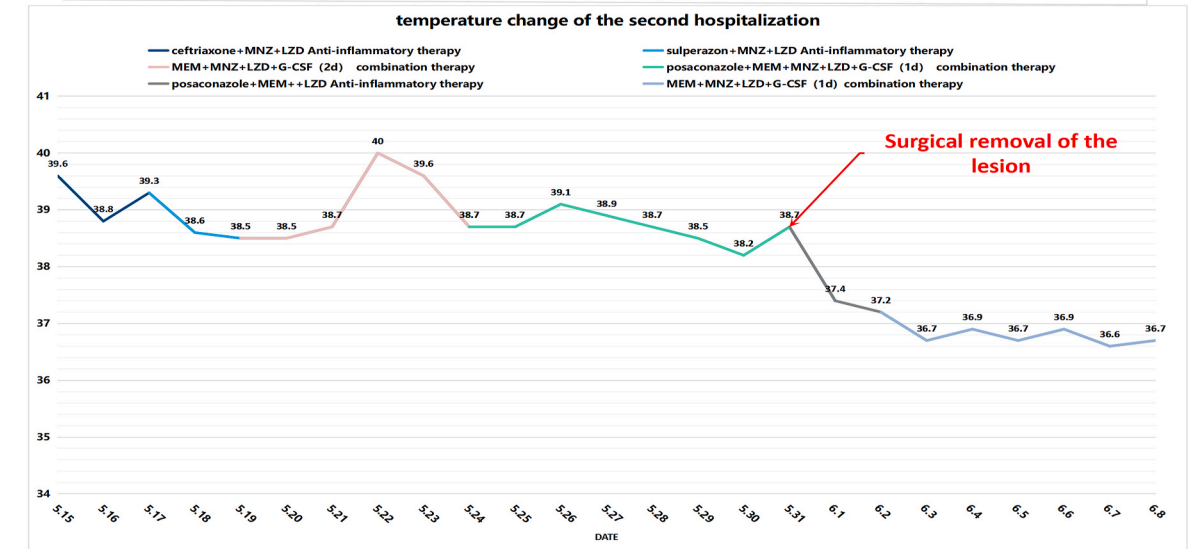
The patient had a history of "pneumonia," "duodenal bulb ulcer," and "erosive gastritis." Three years ago, the patient was admitted for surgical treatment of "septicemia (Staphylococcus aureus infection)" and "infective endocarditis: aortic valve vegetation and aortic regurgitation" (aortic lesion clearance surgery and Ross procedure).

After visiting the hospital, the patient received ceftriaxone anti-infective therapy but with poor control effect. After adding linezolid anti-infective therapy, the patient's fever was controlled (Fig. 2A). During treatment, laboratory tests (Table 2) and imaging results (Fig. 2C) showed that: (1) neutrophils were rare in multiple blood smears; (2) infection markers decreased progressively but could not be restored to normal levels; (3) liver infection lesions persisted and did not show significant reduction; (4) the source of infection was unclear. As the deep visceral infection lesion continued to persist, the family was informed of the risk of recurrent fever, bacterial sepsis, liver dysfunction or even liver failure, abscess dissemination, and they refused further treatment. After discharge, the child was instructed to continue taking oral metronidazole, amoxicillin-clavulanate, and ceftriaxone for treatment.

18 days later, the child returned to the doctor with symptoms of diarrhea for 5 days and fever for 4 days.On admission, physical examination revealed that the liver was 4 cm below the rib margin and there was tenderness on percussion of the liver, but no other positive signs were found. Laboratory auxiliary tests showed that white blood cells were $20.25\hat{}10^9$/L, CRP was 153.62mg/L, procalcitonin was 2.95ng/mL, and ESR was 116mm/h. Abdominal ultrasonography of the liver, gallbladder, pancreas, and spleen showed that the liver infection lesion still persisted and was the same size as before.

After treatment with ceftriaxone, linezolid, and metronidazole anti-infective therapy, the patient's symptoms of recurrent fever could not be controlled despite multiple adjustments to antibiotic therapy (Fig. 2B). We added subcutaneous injection of granulocyte colony-stimulating factor (G-CSF) on top of antibiotic treatment for three days. Although the peak of the fever decreased slightly, it still could not return to normal levels (Fig. 2B). Laboratory tests showed that infection markers had decreased (Table 4), but they were still much higher than normal values. Abdominal MRI findings indicate that the hepatic infection lesion have not reduced but increased in size (Fig. 3B). The hepatic infection lesion demonstrate a more pronounced mass effect compared to previous imaging (Fig. 3A), with compression observed on the liver parenchyma, hepatic veins, portal vein (Fig. 3C), and surrounding structures such as the pancreatic head (Fig. 3D). Genetic testing of the patient revealed a heterozygous mutation in exon 3 of the ELANE gene (Table 3).





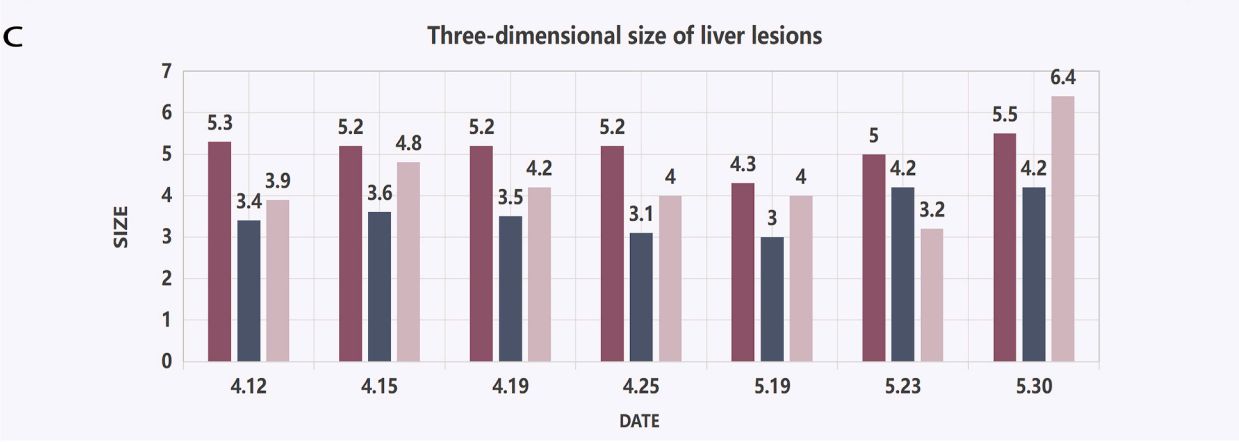


Fig. 2. **(A)**and **(B)** show that the child body temperature changed with antibiotic usage and time during the two hospitalizations. **(A)** Shows that the febrile symptoms in the patient resolved under combined treatment with ceftriaxone, metronidazole, and linezolid. **(B)** Shows that the child had repeated fever during anti-inflammatory treatment and combined G-CSF treatment, and the fever was controlled after surgical treatment. **(C)** Shows the three-dimensional change of the liver infection lesion since the onset of the disease. The size of the lesion did not change significantly during the anti-inflammatory treatment and combined G-CSF treatment.

Table 2
Laboratory auxiliary tests of the first hospitalizationg.

Date	WBC(10^9/L)	CRP(mg/L)	Pathogen detection
4–12	20.02	146.4	Respiratory pathogen multiplex PCR detection (-)
4–13			Throat swab bacterial culture (-)
4–14	14.25	120.19	Stool parasitic examination by microscopy (-)
4–15			EB virus DNA detection(blood); Tuberculin test (-)
4–17			Peripheral blood culture (-)
4–18	14.88	70.83	11 autoantibodies + ANA + ANCA (-)
4–21	17.22	57.45	
4–25	13.39	44.5	

(Detection covers the following types of pathogens. **Respiratory pathogen multiplex PCR detection**：respiratory syncytial virus, influenza A virus (including H1N1 and H3N2), influenza B virus, adenovirus ADV, parainfluenza virus, chlamydia, parechovirus, bocavirus, coronavirus, Mycoplasma pneumoniae;**Autoantibodies detection:**anti-Jo-1antibody, anti-ribosomal protein antibody, anti-SM antibody, anti–SS–A antibody, anti–SS–B antibody, anti-Scl-70 antibody, anti-RNP antibody, anti-centromere antibody, anti-histone antibody, anti-double-stranded DNA antibody, and anti-nucleosome antibody).

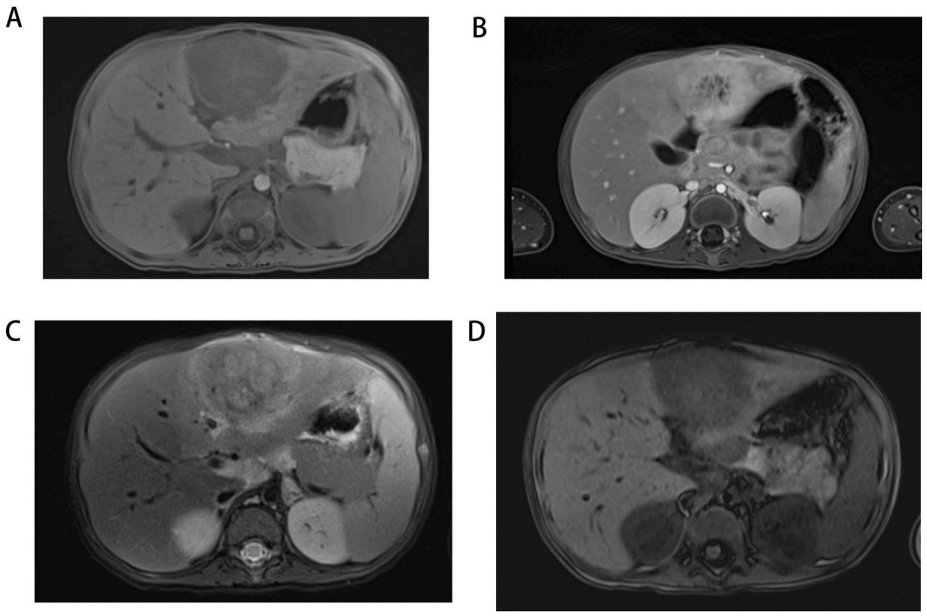


Fig. 3. Abdominal MRI: There is a mass shadow with mixed signal in the SIV segment of liver. **(A)** Shows that the lesion had a certain mass effect, the adjacent liver parenchyma was compressed, and the edge of the lesion was blurred. In **(B)**, the enhanced scan showed that the lesions had honeycomb-like enhancement, and there were narrow-band edema signals with no enhancement around the lesion; the lesion size was 55mm × 42mm × 64mm (left and right × front and rear × up and down). **(C)** Shows that the left portal vein and its branches surrounded the lesion and became thinner under pressure. The left hepatic vein ran through the lesion without clear narrowing. (**D**) Shows that the lesion protruded backward and compressed the head of pancreas, and the splenic vein behind the pancreas head became thinner.

Table 3
Whole exome gene testing of the child.

gene	Chromosome location	Exon of the transcript	Nucleotide/ amino acid	Homozygous/ heterozygous	Normal human frequency	Pathogenicity analysis of ACMG	Disease/phenotype (mode of inheritance)
ELANE	chr19:853 342 {Kawaguch, 2014 #3} {Kawaguch, 2014 #3}	NM_001972; exon3	c.305A > C (p. Q102P)	het	NA	Likely pathogenic	1.Periodic granulocytopenia(AD) 2.Severe congenital neutropenia type 1(AD)

On the 17th day after admission, the patient underwent surgical treatment, namely left hepatic lobectomy, which completely removed the infection lesion. Intraoperatively, a raised white mass was observed in the left hepatic lobe(Fig. 4A), which upon complete excision revealed intact margins of the infectious lesion(Fig. 4F). Upon sectioning the lesion, the hepatic parenchyma was replaced by a

Table 4
Laboratory auxiliary tests of the second hospitalizationg.

Date	WBC(10^9/L)	CRP(mg/L)	Pathogen detection
5–15	20.25	153.62	Stool routine and occult blood (OB) test (-) ; Diarrheal viruses (-)
5–16			Salmonella and Shigella dual-fluorescence PCR detection (-) ; Stool routine and occult blood (OB) test：Fungi, few spores + hyphae observed
5–17	20.4	219.65	
5–18	17.82	194.51	Stool culture (-) ; Toxigenic Clostridium difficile strains (-)
5–20	16.77	156.87	
5–21			Peripheral blood culture (-)
5–22	13.63	139.8	
5–24	17.19	110.61	
5–26	18.22	106.51	
5–29	12.99	78.36	
5–30	12.06	54.99	
5–31	11.39	46.94	
6–1	9.24	66.46	
6–3	8.06	29.29	Purulent material culture from liver lesion: Staphylococcus aureus
6–6	13.13	11.28	
6–7			PICC catheter blood and peripheral blood bacterial culture (-)

(Detection covers the following types of pathogens. **Diarrheal viruses:** enterovirus, human rotavirus antigen, norovirus GI,norovirus GII).

firm yellow-white core with minimal amounts of yellow viscous secretions(Fig. 4E). After surgery, the patient received combined anti-infective therapy with subcutaneous injection of granulocyte colony-stimulating factor (G-CSF) for one day, and the patient's temperature returned to normal, with self-resolving yellowish formed stools. Re-examination of blood infection markers showed a significant decrease to nearly normal levels, and imaging showed that the liver infection lesion had been removed with no residual lesions. One month after discharge, follow-up examination showed that the patient had no recurrence of symptoms such as fever or diarrhea.

Postoperative pathology revealed scattered hepatic structures within the submitted specimen(Fig. 5A), with focal changes consistent with an abscess(Fig. 5B). Culture of purulent material from the center of the liver infection lesion revealed Staphylococcus aureus infection. Based on Illumina sequencing technology, whole-genome high-throughput sequencing of the liver lesion using human genome subtraction technology (HUGO™) indicated that the infection lesion was caused by Staphylococcus aureus, and no other pathogens such as fungi, viruses, or parasites were detected.

3. Discussion

Severe congenital neutropenia (SCN) is a rare genetic immune disease caused by low absolute number of neutrophils (ANC <500) and their dysfunction [1]. Liver abscess is one of the rare clinical outcomes in SCN children following bacterial infections. Pediatric liver abscesses are common in tropical regions, with pyogenic liver abscesses being the most common [4]. In contrast to the pathogens commonly found in adult PLA (such as Klebsiella pneumoniae and Escherichia coli), Staphylococcus aureus is one of the main sources of infection in pediatric PLA reported in most regions, including the United States, Iran and India [5–7]. Common susceptibility factors for pediatric PLA include chronic granulomatous disease, inflammatory bowel disease, diabetes, biliary tract disease, sepsis, appendicitis perforation, liver transplantation [8], etc., but there are few reports considering primary immunodeficiency diseases. It has been reported that neutropenia greatly increases the body's susceptibility to Staphylococcus aureus, and the liver is the first target organ for blood-borne Staphylococcus aureus infection [9]. This article describes an SCN patient with a history of Staphylococcus aureus-induced "septicemia" and "infective endocarditis." We consider this may be a potential source of infection for liver abscess in this SCN patient. However, it should be noted that many Staphylococcus aureus infections are iatrogenic. The possibility of Staphylococcus aureus entering the bloodstream via the skin after measles vaccination, which was administered one week before the onset of fever, should also not be ignored.

The severe reduction in the number and function of neutrophils may be a potential reason for the formation of liver local infection lesions and difficulty in liquefaction in this reported case of SCN patient at our center. Abscess formation is dependent on the interaction between bacteria and neutrophils. Bacteria produce toxins that cause local tissue necrosis, followed by neutrophil infiltration and phagocytosis that kill the bacteria; at the same time, necrosis leads to the release of proteases that liquefy the necrotic tissue to form a cavity filled with pus [10]. Approximately more than 50% of SCN cases are caused by autosomal dominant mutations in the ELANE gene encoding neutrophil elastase. The mutation results in impaired differentiation of neutrophils in children with SCN that not only leads to reduced ELANE expression, but also inhibits neutrophils' ability to restrain bacteria proliferation. In the current case, we identified a missense mutation in exon 3 of the ELANE gene. This mutation was considered as the possible pathogenic source by analysis of the ClinVar database and interpretation of the ACMG guidelines.

Currently, combined antibiotic therapy with daily subcutaneous injection of G-CSF is recommended as the preferred method for severe congenital neutropenia. Combined antibiotic therapy with drainage is the mainstay treatment for pyogenic liver abscesses [11]. However, there is no specific report on the treatment of SCN patients with concurrent liver abscesses. Due to immunodeficiency leading to difficulty in liquefaction of the liver infection lesion, not only is percutaneous drainage impossible and frequent antibiotic

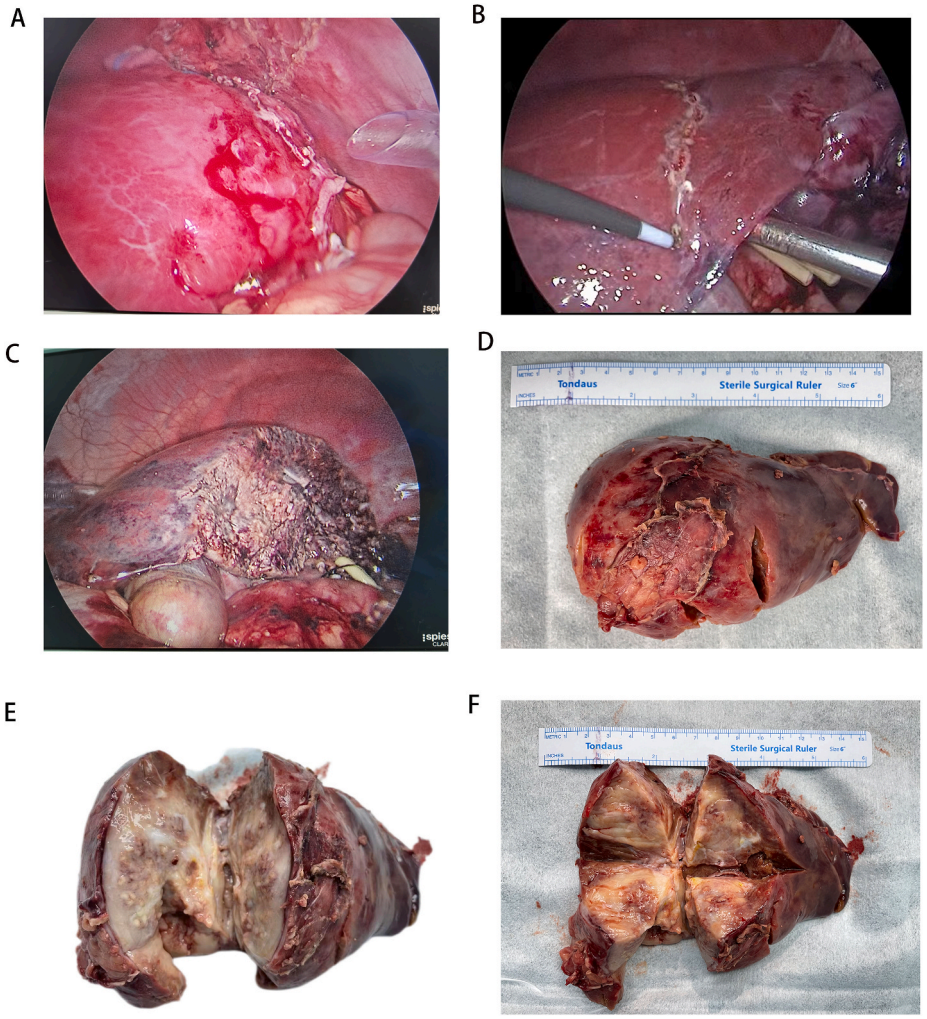


Fig. 4. **(A)** Under laparoscopy, the left hepatic lobe was swollen and hard, and the surface showed a bulging and white mass with inflammatory adhesions of the parietal peritoneum. **(B)** The ischemia line was exposed in the liver after the inflow blood supply, left hepatic artery, and left portal vein supplying the left hemi-liver were completely cut off, and the ischemia line was marked. **(C)** The left lobe of the liver was completely removed, and there was no obvious blood oozing, residual lesions, or necrotic tissue under the naked eye. **(D)** The resected left liver lobe was enlarged and hard. **(E)** The left liver lobe was incised, and the inner core was white and tough, with a small amount of punctate yellow mucous secretions inside. **(F)** After the cross-splitting of the mass, the infection foci were seen. The edge of the infection foci was intact, the mass occupied most of the left liver, and the mas was completely removed.

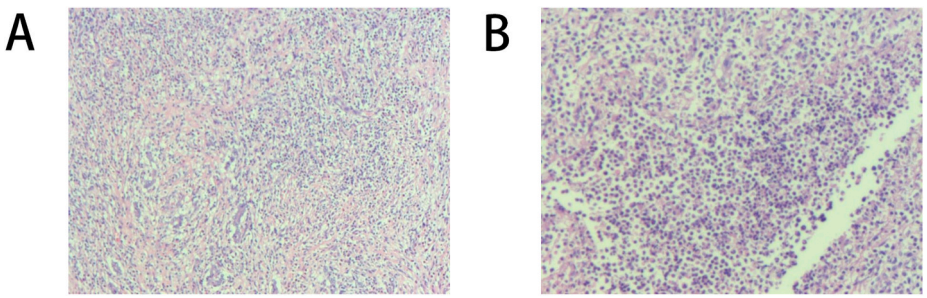


Fig. 5. **Light microscopy findings of the submitted liver tissue:** **(A)** Spindle-shaped fibroid cells were proliferative and collagenized in the center of the lesion; scattered small bile ducts were found in the lesion, accompanied by infiltrations of lymphocytes, plasma cells, histiocytes, eosinophils, and neutrophils. **(B)** Focal neutrophils aggregated to form abscess changes; fibrous tissue proliferation and enlargement were observed in the portal area of the lesion surrounding liver tissue, with infiltrations of lymphocytes, plasma cells and eosinophils.

treatment ineffective, but long-term maintenance of G-CSF treatment significantly increases the risk of antibiotic resistance, dysbiosis, leukemia, myelodysplastic syndrome and other diseases that are dependent on G-CSF dosage. This creates a vicious cycle. Surgical removal of the lesion is an effective way to break this vicious cycle. However, there are almost no reports in the literature on surgical removal of liver abscesses in SCN cases with recurrent fever and persistent refractory symptoms. We present the world's first case report of laparoscopic left hepatectomy with blood flow occlusion for half liver resection in a child with severe neutrophil deficiency complicated with liver abscesses. To prevent the spread of toxin from the inflammatory mass into the bloodstream during the operation, the hepatic blood flow, the left hepatic artery, and the left portal vein supplying the left liver were completely cut off(Fig. 4B). Secondly, the mass was excised along the ischemia marker line from the foot side to the head side; the liver parenchyma was clamped with small-neck forceps, and the middle hepatic vein was completely exposed(Fig. 4C); then, the half liver and the mass were completely removed, with a margin of at least 0.5cm from the mass to avoid local spread if the mass ruptures(Fig. 4D). This surgical approach is the first of its kind in our center. It completely removed the liver inflammatory mass at once while avoiding the risk of bacterial and toxin dissemination by preventing the rupture of the mass during surgery.This patient was also the youngest patient that underwent anatomic hepatectomy. During the 1-month follow-up period, the child responded well to the hepatic lobectomy, and no infection symptoms such as recurrent fever appeared.

4. Conclusion

In children with severe neutrophil deficiency, blood-borne Staphylococcus aureus infection is prone to cause liver abscess formation. A history of Staphylococcus aureus-induced septicemia or vaccination-related iatrogenic operation may be the source of infection. The liver lesion is characterized by difficulty in liquefaction and poor response to antibiotic therapy, requiring a long treatment course. Late-stage complications can easily lead to dysbiosis, multidrug-resistance, and even structural liver damage. Therefore, for children patients who do not respond well to conservative medical treatment, have experienced symptoms for more than half a year, and have incomplete abscess formation, it is recommended to perform anatomical hepatic lobectomy as soon as possible.

Footnotes

This study was approved by Ethics Committee of Shenzhen Children's Hospital (STUDY2020000269).

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Compliance with ethical standards

Consent to Participate : Participants provided their consent to participate in this study.
Consent for Publication : Consent was sought and gained from the participants to publish the findings of this study.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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