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Original Article

Association of asparaginase-associated pancreatitis and ULK2 gene polymorphism

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Abstract: The purpose of the study was to analyze the clinical characteristics and the course of diagnosis and therapy of asparaginase-associated pancreatitis (AAP) in childhood, improve the ability of diagnosis and treatment, and evaluate ULK2 gene polymorphism as a predictive factor for AAP. Data of 12 patients with childhood AAP were reviewed. Sanger sequencing of ULK2 gene was performed in AAP group (n=12) and control group (n=146). The main symptoms of AAP were abdominal pain and vomiting. Generally, the levels of amylase and lipase in the serum peaked within 72 h. Abdominal ultrasonography was performed in 11 patients; seven patients exhibited findings of pancreatic enlargement. Computed tomography was performed in 9 patients. Five patients exhibited findings of pancreatic enlargement and peri-pancreatic exudation. All patients were managed by fasting at the early stage, and seven patients underwent placement of a nasojejunal tube to receive enteral nutrition. One patient underwent endoscopic retrograde cholangiopancreatography (revealing dilation of the pancreatic duct) and endoscopic retrograde pancreatic drainage. Another patient developed signs of shock and received continuous renal replacement. There were no deaths caused by AAP. Therefore, early identification of patients at risk of AAP is of great importance. In addition, repeated elevation in the levels of pancreatic enzymes is indicative of complications. Sanger sequencing analysis of ULK2 gene showed that there was a significant difference of EXON1: -493C>T and EXON1: -308C>G between the AAP group and control group ($P<0.0001$). Thus, ULK2 gene polymorphism may be associated with the development of AAP. However, more validation of this finding is needed.

Keywords: PEG-Asparaginase, asparaginase-associated pancreatitis, children, leukemia, single-nucleotide polymorphism

Introduction

Asparaginase (ASP) is an important drug used in combination chemotherapy against childhood acute lymphoblastic leukemia (ALL) [1, 2]. This agent plays a crucial role in inducing remission and maintaining event-free survival. Pegylated ASP (PEG-ASP) has exhibited advantages over L-ASP [1]. However, acute pancreatitis remains the main complication of treatment with PEG-ASP [3]. Acute pancreatitis occurring after treatment with ASP is defined as asparaginase-associated pancreatitis (AAP) [2, 4, 5]. According to recent data reported by a study investigating a large sample, the risk of pancreatitis associated with PEG-ASP reached 5.9% [2]. However, thus far, no effective predictive biomarkers and preventive measures have been identified [6]. A comprehensive understanding of the clinical features of AAP is important to reduce the rate of mortality among children and improving the safety of PEG-ASP administration. We reviewed a clinical case series of 12 children with ALL who developed AAP during treatment with PEG-ASP at The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Wenzhou, China). The objective of this study was to improve the diagnosis and treatment of AAP and explore the association of clinical risk factors for AAP and ULK2 gene polymorphisms.

Materials and methods

Patients and treatment protocol

From January 2014 to September 2018, 160 patients with childhood ALL were diagnosed

Table 1. Baseline characteristics of patients with and without asparaginase-associated pancreatitis

	AAP group	Control group	*P*-value
Total (n=158)	12	146	
ALL	(7.6%)		
Risk group			P=0.906
LR	5 (7.1%)	65	
IR	3 (6.8%)	41	
HR	4 (9.0%)	40	
Age			P=0.325
1-10 years	9 (6.7%)	125	
10-14 years	3 (12.5%)	21	
Sex			P=1.000
Male	8 (8.0%)	91	
Female	4 (6.8%)	55	
Immunophenotype			P=0.593
B-cell	11 (7.5%)	136	
T-cell	1 (9.0%)	10	

AAP, asparaginase-associated pancreatitis; LR, low risk; IR, intermediate risk; HR, high risk.

and received treatment with the CCLG-ALL 2008 protocol [7]. In 12 of those, ALL was complicated with AAP.PEG-ASP (Jiangsu Hengrui Medicine Co., LTD., Lianyungang, China) (dose: 2,500 U/m^2; maximal dose: 3,750 U) was administered on days 8 and 22 of remission induction therapy, day 6 of consolidation therapy, and days 1 and 15 of delayed consolidation therapy. We excluded two patients due to extensive treatment modifications. The data obtained for 12 patients are listed in **Table 1**.

AAP diagnostic criteria

According to the Atlanta classification [8], at least two of the following three criteria need to be fulfilled for the diagnosis of AAP: (1) Clinical signs and symptoms of acute pancreatitis; (2) Levels of amylase or lipase in the serum >3-fold higher than the upper normal limit; and (3) Imaging findings of pancreatitis.

ULK2 gene polymorphism

Sanger sequencing of ULK2 gene was performed in the AAP group (n=12) and control group (lacking AAP of ALL group) (n=146).

Statistical analysis

All statistical analyses were performed using the SPSS18.0 software (Statistical Product and Service Solutions Inc., Chicago, IL, USA). Differences among subsets (categorical data) were analyzed using the chi-squared test.

Results

Clinical manifestation

AAP occurred after 2-8 doses (median: 2.5 doses), and 1-41 days (median: 14.5 days) from the latest PEG-ASP administration. The development of AAP was observed in the remission induction phase (five patients), consolidation phase (two patients), and late intensification phase (five patients). Clinical manifestations included abdominal pain (n=12), vomiting (n=11), abdominal distension (n=4), shock (n=2), and fever (n=1).

Laboratory and imaging studies

Within 72 h after the diagnosis of AAP, laboratory findings showed a serum amylase level of 125-999 U/L (median: 356.5 U/L; normal range: 30-110 U/L), and a serum lipase level of 175-1923 U/L (median: 333 U/L; normal range: 13-63 U/L). In six patients, the levels of both amylase and lipase in the serum were >3-fold higher than the upper normal limit. In five patients, only the level of lipase in the serum was higher than that limit. Only one patient with enzyme elevations below was diagnosed with AAP through ultrasonography.

Among the nine patients who underwent computed tomography (CT), five patients exhibited findings of pancreatic enlargement and peripancreatic fluid collection, whereas the remaining four patients did not. Eleven patients underwent ultrasonography, showing pancreatic enlargement in seven patients and absence of abnormalities in four patients. Three patients were diagnosed through the presence of symptoms and abnormal levels of amylase and lipase, rather than by ultrasonography and CT (**Table 2**).

Therapy and outcomes

Following the diagnosis of AAP, the patients underwent fasting. In addition, somatostatin and omeprazole were administered to inhibit the production of pancreatic enzymes and suppress gastric acid, respectively. Other conservative treatments included maintenance of the water electrolyte acid-base balance and pro-

Table 2. Laboratory and imaging examinations, treatment and outcomes of 12 patients with AAP

Patient	MVSA (U/L)	MVSL (U/L)	UG	CT		Nasojejunal tube	Abdominal pain alleviated
				Pancreas enlargement	Peri-pancreatic exudation		
1	302	334	+	/	/	+	Yes
2	411	917	+	+	+	+	No
3	543	1105	+	+	+	+	No
4	577	1711	+	/	/	-	Yes
5	158	332	-	-	-	-	Yes
6	757	209	/	/	/	+	Yes
7	999	1923	+	+	+	+	No
8	175	175	+	-	-	-	Yes
9	167	246	-	-	-	+	No
10	223	302	-	-	-	-	Yes
11	125	278	-	+	+	-	Yes
12	609	1491	+	+	+	+	No

AAP, asparaginase-associated pancreatitis; MVSA, maximum value of serum amylase (<72 h); MVSL, maximum value of serum lipase (<72 h); CT, computed tomography; UG, ultrasonography; /, NO execute; Yes, abdominal pain alleviated (<72 h); No, abdominal pain not alleviated (<72 h).

tection of organ function. There were no deaths caused by AAP. One patient (patient 4) expired due to relapse of leukemia. Seven patients received nasojejunal feeding. The condition of one patient (patient 7) rapidly deteriorated, and she developed signs of abdominal distension and shock. She was transferred to the pediatric intensive care unit (PICU) and received continuous renal replacement (CRRT). Fortunately, she has completed all chemotherapy sessions, and been followed-up.

Abdominal pain was alleviated in five patients (patients 4, 5, 8, 10, and 11) within 72 h. The levels of amylase and lipase in the serum were reduced <3-fold the upper normal limit. Oral feeding was reinitiated after 5-7 days, and normal feeding was achieved after approximately 4 weeks. On patient (patient 11) was re-exposed with Erwinia ASP (Guangzhou Baiyun Mountain Mingxing Pharmaceutical Co., LTD., Guangzhou, China) after a normal CT scan, without recurrence of AAP.

In one patient (patient 12), abnormal levels of amylase and lipase in the serum persisted, despite the relief of abdominal pain. After 20 days, CT revealed the presence of a pancreatic pseudocyst (64×47 mm). In the absence of clinical symptoms, clinical observation and continued nasojejunal feeding were recommended. Per os feeding was gradually initiated following the normalization of the levels of amylase and lipase in the serum without recurrence, and chemotherapy was continued with withdrawal of ASP. The pseudocyst was reduced in size after 3 months (34×28 mm) and disappeared after 6 months. The patient entered the maintenance phase of the treatment.

One patient (patient 2) presented with abdominal pain, vomiting, and fever after the administration of PEG-ASP during the delayed intensification phase. Laboratory examinations revealed that the levels of serum amylase and lipase were 3-fold higher than the upper normal limit. CT showed edema of the pancreatic head and neck and peri-pancreatic exudate (**Figure 1**). Following treatment, abdominal pain was relieved. Moreover, following a reduction in the levels of amylase and lipase in the serum below the 3-fold limit without relapse, enteral feeding using a nasojejunal tube was gradually substituted by per os feeding. Unfortunately, this patient experienced an infection after 2 months which resulted in the recurrence of AAP. Consequently, 5 months after the onset of AAP, this patient experienced persistent loss of weight from 28 kg to 20 kg. Re-examination through CT revealed edema in the head of the pancreas, peri-pancreatic exudation, collection of liquid, and pancreatic tube dilation (**Figure 2**). Subsequently, endoscopic retrograde cholangiopancreatography (ERCP) showed dilation of the pancreatic duct, and endoscopic retrograde pancreatic drainage (ERPD) was performed after referral to the Shanghai Shuguang Hospital

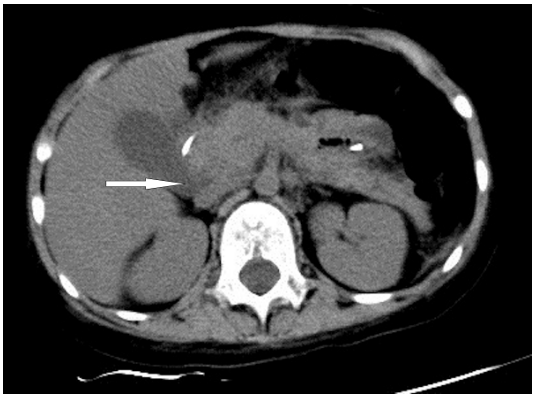

Figure 1. CT showed head and neck of pancreas edema, peri-pancreatic exudate, and ill-defined margins (arrow).

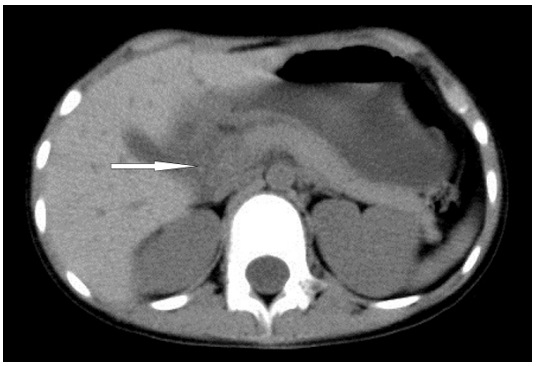

Figure 2. CT image obtained after 5 months showed head of pancreas edema with inhomogeneous density and peri-pancreatic exudate (arrow).

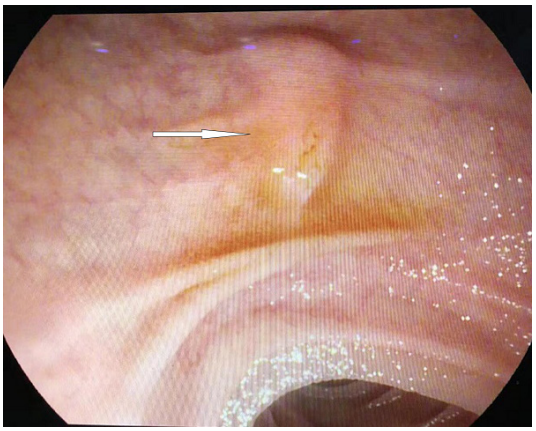

Figure 3. Duodenal papilla was shown under endoscopy (arrow).

(Shanghai, China). During the operation, stenosis was found in the duodenal bulb. ERCP showed the findings of in the head segment of the pancreatic duct stricture. Drainage was initiated after placement of a single pigtail plastic pancreatic stent (**Figures 3**-**5**). One month after surgery, a gradual reduction in the levels of amylase and lipase in the serum was recorded, together with an improvement in clinical conditions. The weight returned to normal levels, 3 months following operation.

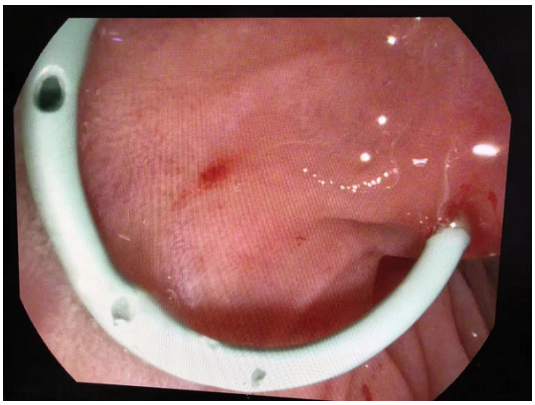

Figure 4. The stent was placed through the duodenal papilla.

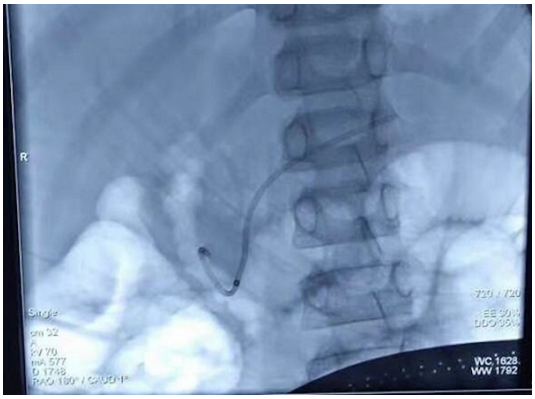

Figure 5. Cholangiography was performed after stent placement.

The association between AAP and ULK2 gene polymorphism

We performed Sanger sequencing of the ULK2 gene in the AAP group (n=12) and control group (n=146).

According to National Center for Biotechnology Information published sequence NM_014683.3, we sequenced all samples using exome sequencing of ULK2 gene. Mutations were found at the following gene loci: EXON1: -493C>T, EXON1: -308C>G, EXON11: +792A>G and EXON14: +1108G>A (**Figures 6**-**9**).

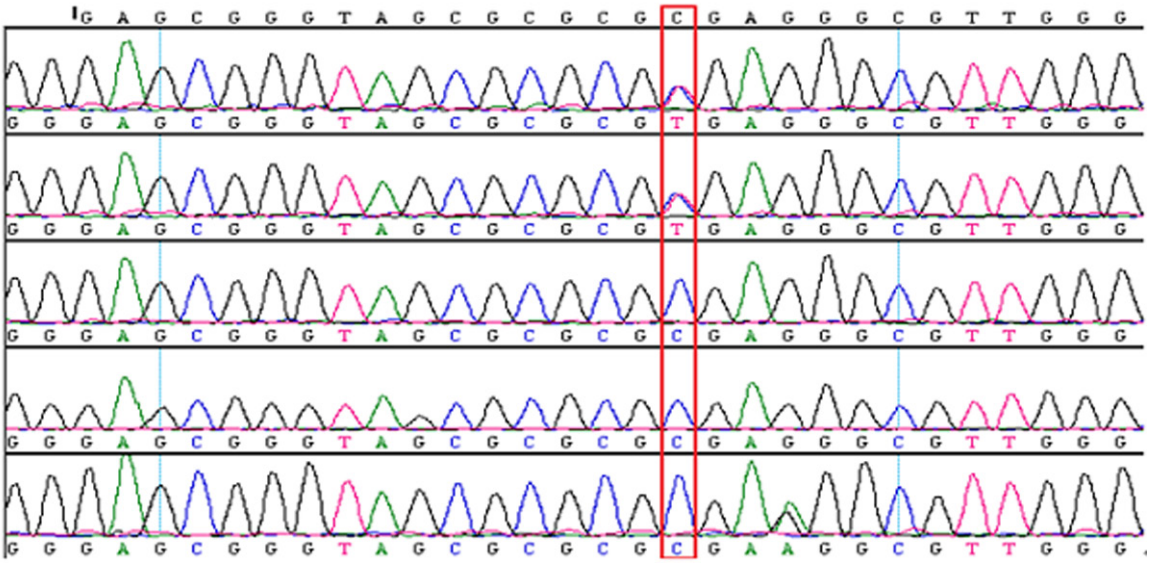

Figure 6. EXON1: -493C>T.

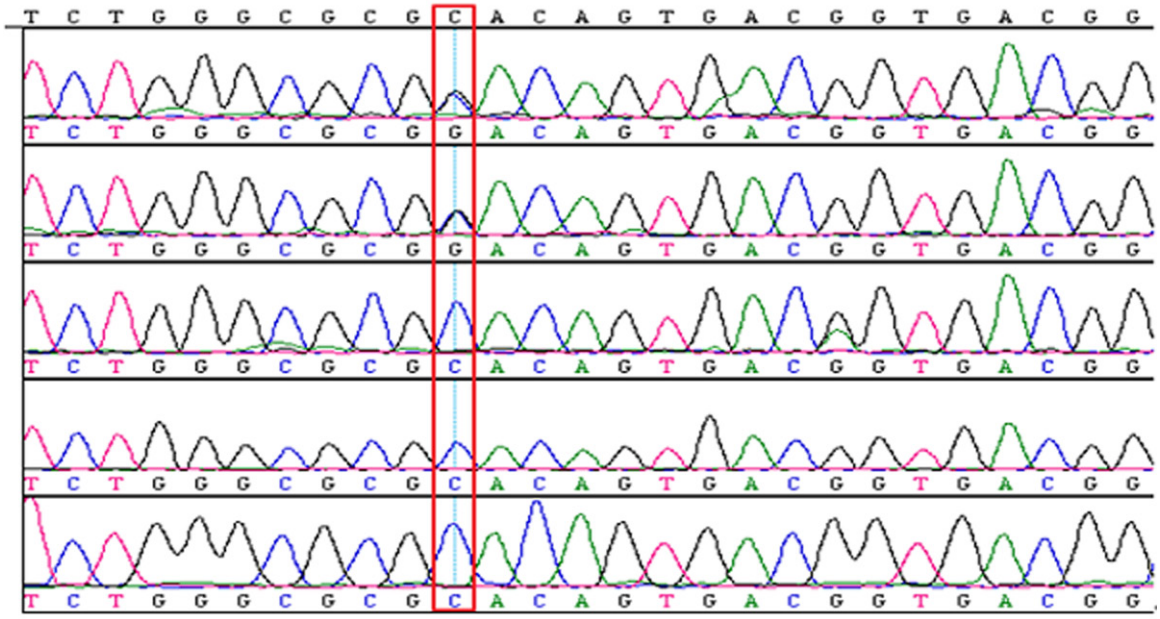

Figure 7. EXON1: -308C>G.

Statistical analysis of the frequency of ULK2 gene mutation

According to the results of Sanger sequencing, the frequencies of ULK2 gene mutation in AAP group and control group are listed in **Tables 3**-**6** respectively. A statistically significant difference of EXON1: -493C>T and EXON1: -308C>G was found between the AAP group and control group (P<0.0001). There is nothing in the literature concerning EXON1: -493C>T and EXON1: -308C>G. However, there was no significant difference of EXON11: +792A>G and EXON14: +1108G>A between the two groups, which might suggest lack of association with disease. Thorough literature search, according to the http://databases.lovd.nl/whole_genome/variants, was performed. The frequency of EXON11: +792A>G and EXON14: +1108G>A mutation was very high in normal populations, but rare

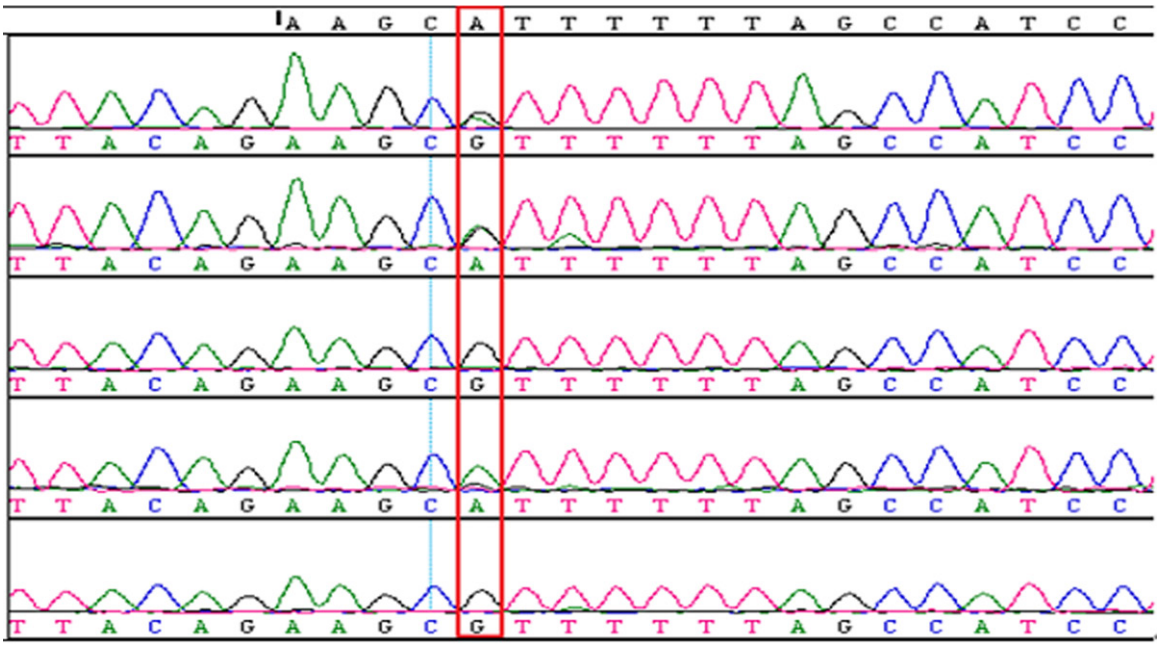

Figure 8. EXON11: +792A>G.

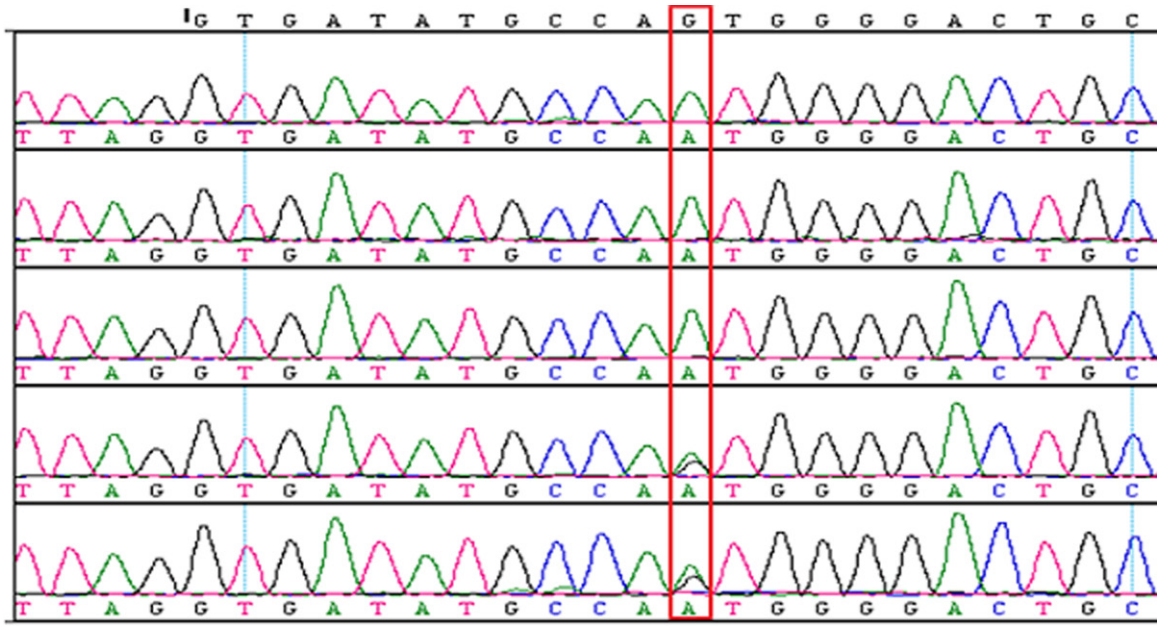

Figure 9. EXON14: +1108G>A.

studies concerning their association with disease have been reported.

Discussion

ALL is the most common childhood cancer, with a 5-year event-free survival rate of 80% [9]. Pancreatitis is a serious complication, and can induce dysfunction in multiple organs. AAP can occur at all phases of chemotherapy with PEG-ASP. However, the exact pathogenesis of AAP remains unclear. Recently, Hashii et al. showed that patients who were administered antacids had a greater incidence of AAP [10]. There was no obvious association between the development of pancreatitis and risk group, sex, leukocyte count at the onset of ALL, and cumulative dose of PEG-ASP. However, associations with

Table 3. Frequencies of ULK2 gene mutation in the AAP group and control group EXON1: -493C>T

	mutation	No mutation	Frequency of mutation	*P*-value
AAP group	11	1	91.7%	P<0.0001
Control group	8	138	5.5%	

AAP, asparaginase-associated pancreatitis; ALL, acute lymphoblastic leukemia; ULK2, unc-51 like autophagy activating kinase 2.

Table 4. Frequencies of ULK2 gene mutation in the AAP group and control group EXON1: -308C>G

	mutation	No mutation	Frequency of mutation	*P*-value
AAP group	11	1	91.7%	P<0.0001
Control group	4	142	2.7%	

AAP, asparaginase-associated pancreatitis; ALL, acute lymphoblastic leukemia; ULK2, unc-51 like autophagy activating kinase 2.

Table 5. Frequencies of ULK2 gene mutation in the AAP group and control group EXON11: +792A>G

	mutation	No mutation	Frequency of mutation	*P*-value
AAP group	11	1	91.7%	P=0.409
Control group	142	4	97.3%	

AAP, asparaginase-associated pancreatitis; ALL, acute lymphoblastic leukemia; ULK2, unc-51 like autophagy activating kinase 2.

Table 6. Frequencies of ULK2 gene mutation in the AAP group and control group EXON14: +1108G>A

	mutation	No mutation	Frequency of mutation	*P*-value
AAP group	11	1	91.7%	P=0.161
Control group	144	2	98.6%	

AAP, asparaginase-associated pancreatitis; ALL, acute lymphoblastic leukemia; ULK2, unc-51 like autophagy activating kinase 2.

the following four factors have been observed [4, 11-15]: (1) Patients aged 10-18 years were linked to a 2.4-fold increased risk of developing AAP versus younger patients. In the present series, patients aged 10-14 years showed an association with a 1.87-fold increase in the risk of developing AAP compared to those aged <10 years. (2) Combined administration with other drugs (e.g., 6-mercaptopurine, daunomycin, and prednisone) can increase the risk of AAP occurrence, as can (3) the presence of an idiosyncratic genetic gene, or (4) the presence of severe hyperlipidemia. Moreover, Sanger sequencing analysis of ULK2 gene was conducted in 12 patients. The results revealed that EXON1: -493C>T and EXON1: -308C>G mutation rate in the AAP group was significantly higher when compared to the control group (P<0.0001). These results might indicate that ULK2 gene EXON1: -493C>T polymorphism and EXON1: -308C>G polymorphisms were associated with the occurrence of AAP, but the number of cases in this study is limited and further validation is needed.

In this study, the main clinical manifestations included abdominal pain and vomiting. The development of abdominal pain and vomiting during chemotherapy with PEG-ASP is indicative of AAP occurrence. Therefore, it is necessary to monitor the levels of pancreatic enzymes in the serum and perform imaging examinations. Although elevation of the levels of amylase or lipase in the serum was invariably associated with the occurrence of AAP, the degree of elevation did not correlate with the severity of pancreatitis [10]. Data in this study showed that, in one patient, the levels of amylase and lipase in the serum were not >3-fold higher than the upper normal limit at the time of AAP diagnosis. The levels of amylase and lipase gradually decreased in 10 patients along with improvement in the general condition. However, these levels were repeatedly increased in two patients; one with a pseudocyst and the other with stricture and distortion of the main pancreatic duct in the head of the pancreas. Monitoring through imaging examination is necessary for children with persistent or deteriorating clinical symptoms, as well as persistent elevation of the levels of amylase and lipase in the serum.

Abdominal ultrasonographic examinations and CT can be used to support the clinical diagnosis of AAP. Compared with CT, abdominal ultrasonography can prevent exposure to radiation and it is easier to use at the bedside. However, the results can be affected by obesity and intestinal gas. In the present study, the structure of the pancreas was distorted in ultrasonographic imaging due to the presence of intestinal gas, whereas CT showed clear characteristic imaging changes in the pancreas. Therefore, it is reasonable to reserve the use of CT for

patients with typical clinical symptoms and laboratory findings of pancreatitis, as well as normal ultrasonographic imaging findings.

In this study, all 12 patients received conservative management including fasting, administration of somatostatin, acid suppression, and correction of electrolyte turbulence. In the early phase of AAP, gut rest is essential; however, the optimal fasting time remains uncertain [16]. According to the data examined in this study, ≥3 days of fasting are required. Moreover, children showed good tolerance of the nasojejunal tube, which can be used as the primary means for the administration of short-term enteral nutrition in patients with AAP. Severe acute pancreatitis is a life-threatening condition, characterized by systemic inflammatory responses and resultant dysfunction of multiple organs. CRRT eliminates inflammatory mediators, regulates fluid and electrolyte imbalance, maintains the balance between acid and base, and effectively reduces damage to the kidney and other organs [17]. In this study, one patient (patient 7) was treated with CRRT in the PICU, showing a favorable therapy outcome.

AAP complicated with pancreatic pseudocyst often occurs within 1 month [18]. The presence of a pancreatic pseudocyst is typically mild and self-limiting; little surgical intervention is needed. Spraker et al. [16] showed that, in five AAP patients complicated with a pancreatic pseudocyst, the pseudocyst resolved after 3-37 months of nonsurgical management. In this study, one patient (patient 12) with AAP developed a pancreatic pseudocyst after 20 days. The abdominal imaging examination showed spontaneous resolution of the pseudocyst after nonsurgical management; however, it was suggested that the observed decrease in size was slow. The sample size of this study was limited; hence, more clinical data are required.

In cases of recurrent AAP, attention should be paid to the development of pancreatic duct stricture. One patient (patient 2) experienced recurrence of AAP within 5 months and weight loss of 8 kg. Subsequently, ERCP revealed that this patient developed main pancreatic duct stricture in the head of the pancreas. One month after undergoing ERCP, dilation of the pancreatic duct, and ERPD, the clinical symptoms of this patient were alleviated. Moreover, the levels of amylase and lipase in the serum returned to normal values, and the patients regained weight after 3 months.

The feasibility of re-exposure to ASP after the development of AAP is a matter of concern. Numerous patients redevelop AAP upon re-exposure to ASP; however, the rate of ALL relapse was increased after discontinuation of treatment with ASP [19-21]. Therefore, it is important for clinicians to distinguish between patients who may be re-exposed to ASP after the development of AAP and those who may not. Raja et al. [2] found that re-exposure to ASP in patients with mild AAP tended to be safe. Mild AAP is defined as follows: (1) duration of symptoms <72 h; (2) levels of amylase or lipase in the serum <3-fold the upper normal limit within 72 h; and (3) absence of a pseudocyst, hemorrhage, and necrosis determined by imaging examination. In this study, at the time of admission, one patient (patient 11) presented with a leukocyte count >100×10^9/L and MLL-AF4(+) fusion gene. These findings suggested that this patient belonged to the high-risk ALL group. The patient developed mild AAP during the consolidation period. In the subsequent chemotherapy, PEG-ASP was substituted in favor of Erwinia ASP to avoid the relapse of ALL. The treatment was uneventful, without a recurrence of AAP.

Therefore, treating physicians should pay attention to clinical symptoms of patients (i.e., abdominal pain, vomiting, levels of amylase and lipase in the serum) during the period of chemotherapy with PEG-ASP. Once the development of pancreatitis is suspected, pancreatic imaging examinations should be performed. Early identification of AAP is important for improving therapy outcomes related to AAP. Combination management with other medical departments (i.e., pediatric gastroenterology and PICU) is also important to improve the treatment of AAP. We also found that ULK2 gene EXON1: -493C>T polymorphism and EXON1: -308C>G polymorphism were associated with the development of AAP. This study is limited because it is a relatively small observational study, so further validation is required.

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Disclosure of conflict of interest

None.

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