CASE REPORTS

ACUTE PANCREATITIS DURING L-ASPARAGINASE TREATMENT IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

L-asparaginase (L-ASPA) has been put to a wide application in many therapeutic protocols, above all in the treatment of acute lymphoblastic leukemia (ALL). We presented three cases of acute pancreatitis in children with ALL induced by administration of L-ASPA preparations. Our observations revealed that ultrasound investigations are very useful in diagnosis and monitoring changes in the pancreas. The use of L-ASPA derivatives allows to decrease the toxic and allergic sequele resulting from the administration of the drug.

INTRODUCTION

L-asparaginase (L-ASPA) is an enzyme (aminohydrolase) obtained from bacterial strains *Escherichia coli* or *Ervinia carotovora* and *Ervinia chrysanthemi*. The antineoplastic mechanism is based on the decomposition of L-ASPA, the aminoacid required for protein synthesis and growth of neoplastic cells, into asparagine acid and ammonia (Opolski, 1981; Orzechowska-Juzwenko, 1990; Pietras, 1996). L-ASPA has been put to a wide application in many therapeutic protocols that are used at present, above all in the treatment of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphomas (NHL) (Orzechowska-Juzwenko, 1990; Rokicka-Milewska, 1992). The use of this drug is restricted to some extent, however, by its side effects. The most frequent complication following L-ASPA obtained from E. coli strain is found to be abdominal pain and allergic reactions (Clavell, 1986; Rokicka-Milewska, 1992). According to Rokicka-Milewska, they occur irrespective of the negative result in the previously performed allergic test (Rokicka-Milewska, 1992). After erviniase has been administered, the side effects are found to occur less frequently and are limited to allergic reactions of slight intensity (Rokicka-Milewska, 1992). One of ma-jor complications following the use of L-ASPA preparations is acute pancreatitis (Chambon, 1993; Clavell, 1986; Filiks-Litwin, 1996; Krasowska, 1987; Niemeyer, 1991; Orzechowska-Juzwenko, 1990; Pietras, 1996; Rokicka-Milewska, 1992; Tatoń, 1985). The incidence of drug-induced pancreas failure including one induced by L-ASPA, is estimated at 3-8% (Niemeyer, 1991; Weizman, 1988). It results from direct toxicity and/or negative effect of L-ASPA deprivation on the whole protein metabolism of the organism leading to a disturbed synthesis of, among others, albumins, fibrinogens, plasma blotting factors IX and X, plasminogens, and antithrombin III (Bradkiewicz, 1995; Dobaczewska, 1998; Pietras, 1996; Skomra, 1992). Acute pancreatitis is clinically manifested by abdominal pains, diarrhoea, vomiting. In order to establish a diagnosis, it is useful to perform activity determinations of amylase, lipase and lactate dehydrogenase (LDH) in blood serum as well as urine amylase. Moreover, it is also helpful to determine C-reactive protein (CRP) concentration in blood serum (Chambon, 1993). Results obtained from imaging investigations prove to be extremely important. The ultrasound picture demonstrates most frequently enlargement and oedema of the organ, decreased echogenicity, and sometimes cystoid changes (Chambon, 1993; Ojala, 1997). In the latter case, a precise determination of changes is made possible by the use of computer tomography (CT)

(Chambon, 1993). Treatment of pancreatitis in the course of L-ASPA therapy is conservative, and in selected cases - operative (Balcerska, 1998; Barra, 1990; Chambon, 1993; Filiks-Litwin, 1996; Ojala, 1997; Rokicka-Milewska, 1992). It should be noted here that there is a possibility of diabetes, which is caused by failure of the endocrine part of pancreas (Balcerska, 1998; Pastore, 1984; Pietras, 1996; Skomra, 1992; Wang, 1993). The issue is discussed in a separate report (Stencel, 1998).

The present study is aimed at presenting cases of pancreas failure in children with ALL treated with L-ASPA preparations, demonstrating changes observed in ultrasound investigations, and indicating those symptoms which would enable an early identification of patients with a risk of pancreas failure who require a rapid intensive therapy.

MATERIALS AND METHODS

Case 1

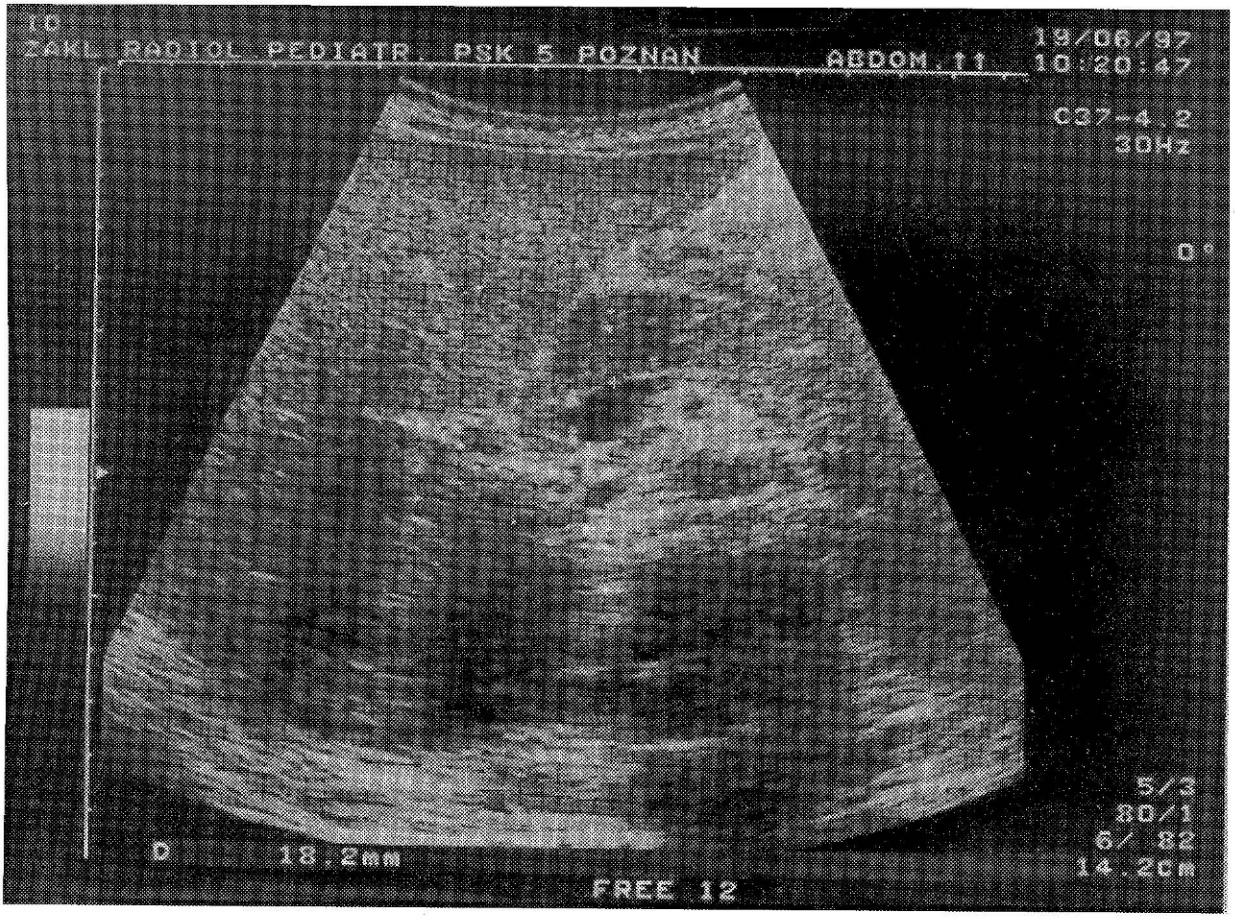

Fig. 1. Case 1, enlargement of the liver and the pancreas (body – 1,8 cm) with normal echogenicity, free fluid in the peritonea cavity.

L.W. (case history 5310/97) - an 8-year-old boy with the common type ALL of the standard risk group (SRG) with IR=1.6.
Chemotherapy was commenced according to ALL-BFM 90 trial modified according to Polish Pediatrics Leukemia/Lymphoma Study Group (PPLLSG). The drug doses were calculated with reference to the child's body area (1.0 m^2): Prednisone (PSL) - 60mg/m^2 p.o administered daily in 2 doses, Vincristine (VCR) - 1.5 mg/Fm^2 i.v. every 7 days, Daunorubidomycine (DNR) - 30 mg/Fm^2 i.v. every 7 days, Kidrolase (L-ASPA) - 10,000 u.m. L/m^2 i.v. every 2 days. Initially, the treatment did not cause any complications. On the 22nd day in the induction of remission, following the sixth administration of L-ASPA (total dose - 60,000 u.m.), the patient manifested severe abdominal pains, loose stools, vomiting. The objective examination revealed drum belly, tenderness at palpation in the projection of the stomach, without peritoneal signs, normal peristaltics.

Auxiliary investigations showed a low fibrinogen level (below 50 mg%), increased inflammatory exponents (CRP - 3.55mg%), high LDH level - 364 u.m./l, normal amylase levels in blood serum and urine, normal level of glycemia. Abdominal ultrasound investigations demonstrated enlargement within the body of the pancreas, and features of pancreatitis (Fig. 1). The dietary treatment was used together with antibioticotherapy, fibrinogen's substitution, Trascolan, symptomatic drugs (Buscolizyna, Zantac, infusion fluids), which resulted in improved general state, subsidence of symptoms, and normalisation of ultrasound pictures on the 11th day of treatment. Due to the episode described above, administration of the remaining two doses of L-ASPA was discontinued. At present, the patient is in the first haematological and clinical remission of leukemia undergoing supportive chemotherapy.

Case 2

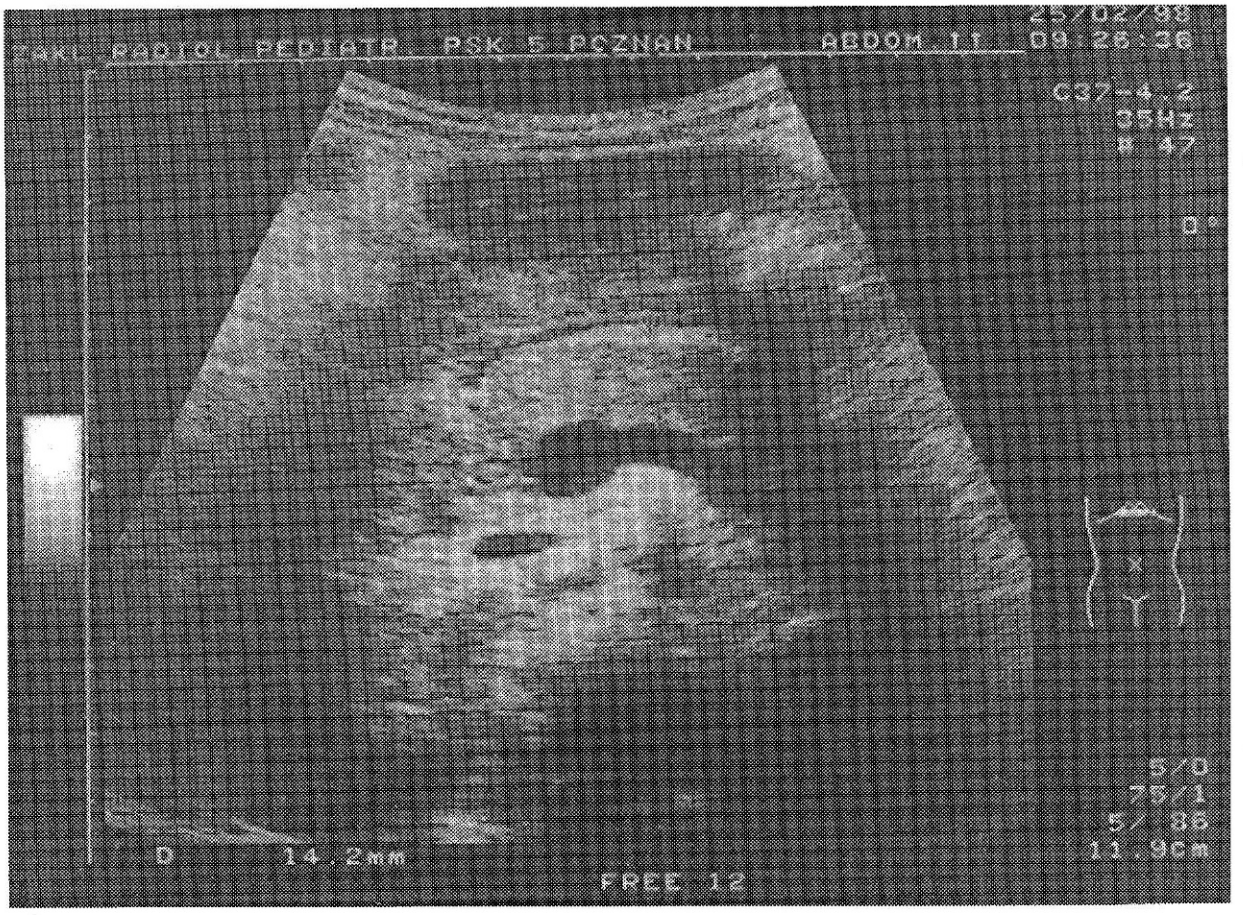

Fig. 2. Case 2, enlargement of the pancreas (head – 1,1 cm; body – 1,4 cm) with increased echogenicity, free fluid in the peritoneal and pleural cavity.

N.L. (case history 1398/98) - a 7.5-year-old girl with diagnosed the common type acute lymphoblastic leukemia, which belonged to the standard risk group with IR=1.22. Induction of remission was commenced according to ALL-BMF 90 Protocol. Doses of drugs (Prednisone, Vincristine, Daunorubidomycine) were established calculating the patient's body area 1.0m^2 Moreover, an oral prevention of infections was used (Nystatyna, Biseptol, Colistin). On the 19th day of induction (i.e. following the third dose of Kidrolaze - total dose 30,000u.m.), the patient manifested abdominal pains and loose stools. The objective examination revealed soft abdomen, tenderness at palpation in the projection of the stomach, lack of peritoneal symptoms, normal peristaltics. Auxiliary investigations showed increased levels of glycemia (125-170 mg%), high inflammatory exponents (CRP - 4.22 mg%), LDH - 893 u.m./l, leukopenia (200 G/l), hypofibrinogenemia (below 56 mg%), hypoproteinemia (3.97 g%), hyperuricemia (14.8 mg%), and increased levels of urea (83 mg%). There were no increased levels of amylase in blood serum and urine. The ultrasound investigation revealed the enlarged hyperechogenic pancreas with the following

dimensions: head - 18 mm, body - 12 mm, tail - 14 mm without widening of the Wirsung duct, and with homogenous parenchyma, significant quantity of free fluid in the peritoneal cavity, and enlarged kidneys of intensified cortex echogenicity and increased cortico-spinal differentiation. (Fig.2). Intensive dietary therapy was used in association with antibioticotherapy (Cefotaksym, Dalacin, Vancocin, Diflucan), blood derivatives (CPAG, plasma, albumins, Bioglobulin), symptomatic drugs, and infusion fluids, which, on the 16th day of treatment, resulted in improved clinical state, normalisation of laboratory and imaging results. The chemotherapy was continued replacing Kidrolaze with Erviniase. The treatment continued without any complications.

Case 3

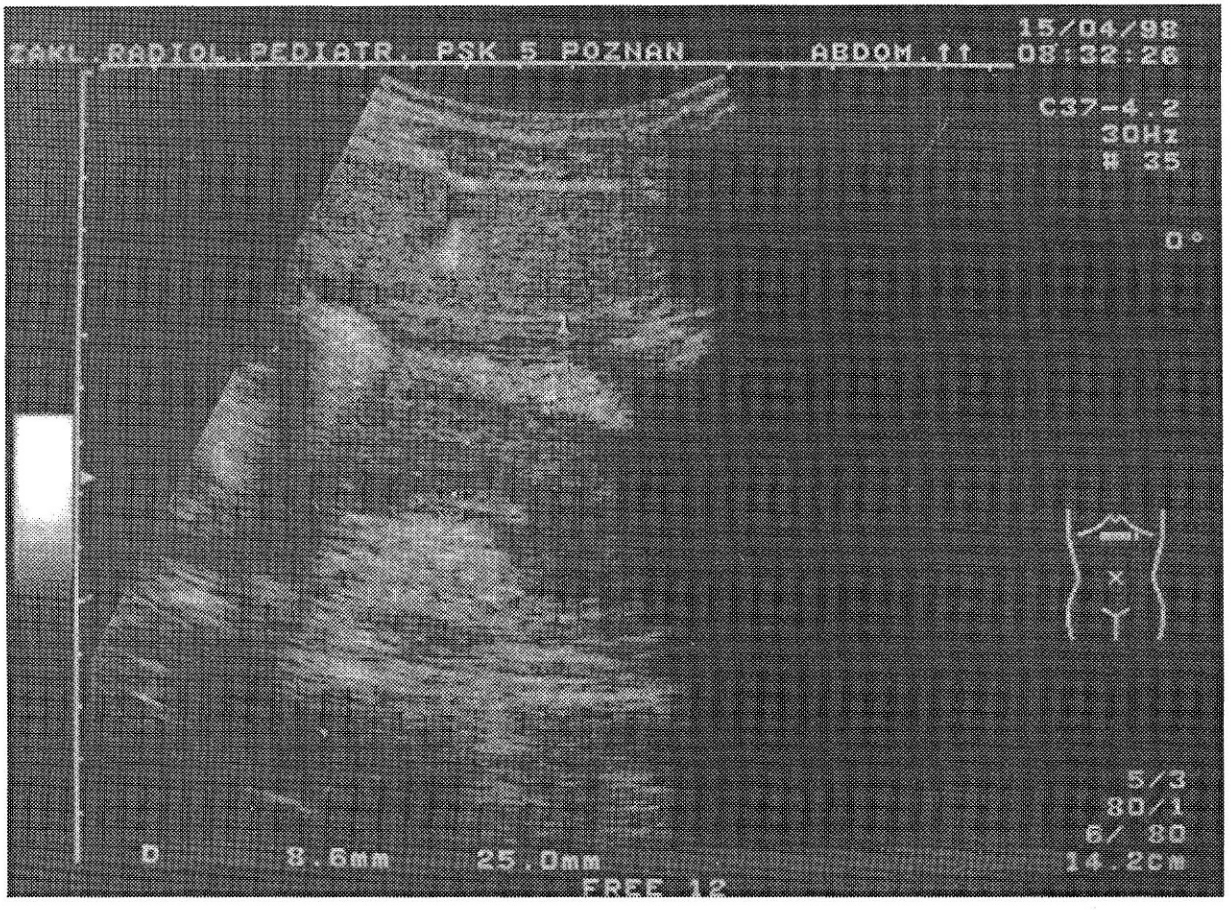

Fig. 3. Case 3, the hyperechogenic, enlarged pancreas (body, tail – 2,5 – 2,7 cm), blurred outline of the anterior capsule homogenous pancreatic parenchyma, free fluid in the peritoneal cavity.

K.B. (case history - 4205/98) a 10-year-old boy with infantile cerebral palsy. T-cell acute lymphoblastic leukemia was diagnosed, belonging to the high risk group. The induction of remission was commenced according to New York Protocol. Five days after the first administration of VCR, the patient manifested severe abdominal pain. In the objective examination, drum belly with diffuse tenderness at palpation, and hypoperistaltics without peritoneal symptoms were observed. Radiological investigations revealed faecal impaction, and symptoms of low obstruction. The above mentioned symptoms subsided after a single administration of prokinetic drugs (Ubretid). On the 5th day after the first administration of Kidrolaze according to remission consolidation (dose of 30,000 u.m., total dose of four Kidrolaza administrations - 120 thousand u.m.), the patient manifested severe abdominal pain. At admission to the Clinic, the patient had a serious general state. The severe pains were accompanied by paleness of skin inguments, hypotension, tachycardia, filiform pulse. The objective examination revealed diffuse abdominal tenderness was accompanied by hypoperistaltics without observed peritoneal symptoms.

In the auxiliary investigations, the following results were obtained: serum diastase - 524.8 U/l, plasma lipase - 2153 U/l urine

diastase - 3753 U/l, CRP - 3.7 mg%, glucose - 318 mg%, Hb - 12.1 g%, leukocytes -12.0 G/l, thrombocytes - 520 G/l. The USG investigations revealed features of acute pancreatitis (Fig. 3). The therapeutic treatment included a stomach tube, Sandostatin 0.05mg - three times daily subcutaneously, Trascolan - 4 x 100 thousand u., analgesics (Tramal, Pyralgin), anti-infectious drugs (Fortum, Metronidazol, Sandoglobulin). In view of the suspected onset of intravascular clotting (decreased number of thrombocytes, positive paracoagulation tests, increased FDP), the therapy included also heparin in the dose of 4 x 1000 u. In order to obtain normal diuresis at pertinent blood pressure of 70/40, 4ug/kg/min dopamine was included. Complete parenteral nutrition was used (glucose drip infusion contained insulin due to hyperglycemia). After a 24-hour period, there was already a considerable improvement of the clinical state (diminished pain sensation, normalised blood pressure, DIC was excluded). After seven days, the diastin level was found to reach a normal range, Sandostatin and Trascolan administration were discontinued. Due to the described reaction, administration of further doses of Kidrolaze was discontinued. The patient continued chemotherapy.

DISCUSSION

Despite the increasingly more positive results even in the highest risk groups, treatment of acute lymphoblastic leukemia is still found to cause many problems. The intensity of antileukemic therapy proves to be causing occurrence of a series of complications which, by themselves, constitute a danger to the child's health and life. One of the complications induced by the administration of cytostatic drugs is acute pancreatitis (AP). This rare disease in the population of children and adolescents (10-15/100 000) (Barra, 1990) is found to occur as a drug-induced complication in 3-8% patients (Niemeyer, 1991; Weizman, 1988) whereas among those receiving L-asparaginase preparations - in 2-2.5% (Filiks -Litwin, 1996).

In the reported three cases, AP was induced by administration of L-asparaginase preparations, and was characterised by some common features. The onset of the first symptoms occurred on the 22nd, 19th and 33rd day of the therapy following the 6th, 3rd and 4th dose of the drug, respectively (total doses: 60000 , 30000 and 120 000 u.m., respectively). It is in agreement with reports of other authors observing occurrence of AP following L-asparaginase between the 2nd day and 10th week from the administration of the drug (Filiks-Litwin, 1996). The patients reported typical complaints, predominant abdominal pains of various intensity were found in all the cases. In 2 patients, loose stools were reported and in 1 patient, additionally vomiting.

The objective examination revealed tenderness at palpation in the projection of the stomach without peritoneal symptoms or disorders of peristaltic movement. Only in one case (patient K.B.), the course of the disease was more intensive with observed hypoperistaltics and traumatic symptoms in the form of tachycardia and decreased arterial blood pressure. Disorders of peristaltics, and metoerism previously observed in the patient, are associated with intravenous administration of vincristine (VCR). The subjective and objective changes observed in our patients did not differ from those reported by other authors (Balcerska, 1998; Barra, 1990; Bukowska, 1995, Chambon, 1993; Pietras, 1996; Rokicka-Milewska, 1992, Weizman, 1988).

Results of the auxiliary investigations demonstrated in all the patients slightly increased CRP values (3.55 - 4.22 mg%), in 2 cases - decreased fibrinogen levels and hyperglycemia, in 1 case requiring the intravenous administration of insulin. Since in patient K.B., features of intravascular clotting were observed, heparin was administered. It should be noted that there were no changes in serum and urine amylase levels in 2 patients. Only in 1 patient, the amylase level exceeded the levels indicating AP i.e. >500U/l in serum, and >2300 U/l in urine (Barra, 1990) (524.8 and 3753 U/l respectively). It concerned the patient with the most serious course of the disease following the administration of the largest dose of L-asparaginase. According to the data obtained from the literature, in 1/3 patients with AP there is no increase of amylase serum or urine activity (Barra, 1990), and the presented cases are found to confirm the observation (although there was no possibility to carry out statistical analysis). Clavell describes the so called transient hyperamylasemia syndrome which is a laboratory equivalent of AP. It is a transient (48-72 hours) increase of blood serum amylase levels (less than a 10-time or usually even less than a twofold increase) with no evident exponents of pancreas failure (Clavell, 1986). It can be inferred that in the course of differentiation of the causes of abdominal pains in the child with neoplastic disease, obtaining normal serum and amylase levels is found not to exclude unambiguously the occurrence of AP whereas the increased levels are not pathogenic. It makes it necessary to seek other

methods useful in diagnosing and differentiating AP. It seems that abdominal ultrasonography may turn out to be such an investigation.

In our patients, the most frequently observed changes in the ultrasound investigation were enlargement of the pancreas and changes in its echogenicity (both an decrease as well as an increase) and presence of the free fluid in the peritoneal cavity. It should be emphasised that the ultrasound picture in AP is not homogeneous. The character and intensity of the changes depend on the clinical form and progression of AP (Table 1). Correct interpretation of the ultrasound image is therefore possible only in connection to the clinical picture, results of auxiliary investigations and in reference to specially prepared population norms (Table 2, Table 3). In view of the described possibility of a lack of changes in amylase activity, the ultrasound investigation becomes extremely useful in early detection and differentiation of AP with cholelithiasis and inflammation in the billiary system, nephrolithiasis and other acute abdominal diseases, and when it is performed serially, it also proves to be a very significant element of monitoring the course of the disease.

1. Homogenous echostructure typical of organs with parenchymal structure.
2. Echogenicity depending on child's age and amount of fatty tissue in the stroma up to 10 years of age usually not bigger than the echogenicity of the liver.
3. Smooth edges, sharp separation from environment.
4. The Wirsung duct invisible or visible only within the body width up to 2 mm.

Table 1. Picture of normal pancreas in the ultrasound investigation.

Age	Pancreas dimensions		
	head	body	tail
0-6 years	1.6	0.7	1.2
7-12 years	1.9	0.9	1.4
13-18 years	2.0	1.0	1.6
AP	2.2-4.0	0.8-2.0	1.4-3.5

Table 2. Normal dimensions of the pancreas in children (cm) according to Coleman (7).

1. Focal or diffuse enlargement of the pancreas.
2. Decreased echogenicity of pancreatic parenchyma reflecting oedema, rarely increased echogenictity as a symptom of necrosis.
3. Sometimes widening of the Wirsung duct.
4. False cysts.
5. Free fluid in the peritoneal cavity sometimes in the left pleural cavity.

Table 3. Diagnostic criteria for acute pancreatitis in the ultrasound investigation.

Treatment of our patients included complete parenteral nutrition, which was linked to insertion of a stomach tube in 1 case, antibiotics and symptomatic drugs. In the most serious case, it was necessary to administer Sandostatin, Dopamine, Heparin and Insulin. The therapy lasted 11, 16, and 7 days, respectively. In all the cases, we achieved restitution, subsidence of clinical symptoms and deviations in the objective state, normalisation of laboratory results, and normal ultrasound pictures of the pancreas. In 1 patient, after the administration of two consecutive doses of L-asparaginase was given up, the chemotherapy with Kidrolaze was continued, in 1 - Erviniase was introduced interchangeably, and in K.B. who manifested the most intensive course of AP, further administration of L-asparaginase preparations was discontinued. Other authors also point to the fact that there is a possibility of a complete subsidence of AP without complications following a conservative treatment, and thus enabling continuation of the antileukemic therapy (Balcerska, 1998; Barra, 1990; Chambon, 1993; Filiks-Litwin, 1996; Rokicka-Milewska, 1992). In order to avoid or decrease the toxic or allergic complications induced by the administration of L-asparaginase preparations, new derivatives of these drugs are now being developed. An example could be a combination of L-asparaginase with polyethylene glycol (Oncaspar) which so far has been administered in a small group of patients and has yielded good results (Sikorska-Fic, 1998).

CONCLUSIONS

1. In the diagnosis and differentiation of causes of abdominal pains in patients with neoplastic diseases, particularly in the course of the therapy with L-asparaginase preparations, it is necessary to include pancreatitis.
2. In the course of AP, changes in the blood serum and urine amylase activity may turn out to be small or may not occur at all.
3. Ultrasound investigations prove to be very useful in diagnosis and monitoring of changes in the pancreas.
4. The Ultrasound picture is heterogeneous according to the variety of clinical forms and clinical progression of AP.
5. The role of the ultrasound investigation includes also early detection of complications, and differentiation with cholelithiasis and inflammation in the biliary system, nephrolithiasis and other acute diseases in the abdominal cavity.
6. In the majority of cases, early commencement of appropriate conservative therapy allows to obtain complete subsidence of changes and thus to continue the therapy.
7. The use of Erviniase-derived preparations as well as L-asparaginase derivatives allows to decrease the toxic and allergic sequele resulting from the administration of the drug.

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