

What is the result: chylous leakage following extensive radical surgery of neuroblastoma

Yin Liu, Ci Pan, Jing-Yan Tang, Jing Chen, Min Zhou, Qi-Dong Ye

Shanghai, China

Background: Postoperative chylous leakage is a rare complication that results from disruption of either mediastinal or retroperitoneal lymphatic channels during dissection or from obstruction by original lesions such as a malignancy. There is lack of clinical experience in pediatric patients about how to manage the leakage and what the result will be.

Methods: We retrospectively analyzed the clinical outcomes of 5 children with neuroblastoma (NB) (stage 4 in 4 children and stage 1-2 in 1 child) who had received non-surgical treatment of chylothorax and/or chylous ascites after retroperitoneal/posterior mediastinal extensive radical resection of NB for complete tumor removal. Conservative therapy with low-fat diet, medium-chain triglyceride and/or total parenteral nutrition was the mainstay treatment for chylous leakage.

Results: Four of the 5 children recovered after 6-32 days of conservative treatment, and the last one who did not respond was cured by surgical management for chylous fistula 45 days after primary surgery. Postoperative imaging showed that more than 90% of tumors were resected and all of them showed very good partial remission (VGPR). Among the 4 patients in stage 4, 3 relapsed after radical resection of NB. The patient of stage 1-2 was still in VGPR.

Conclusions: The majority of patients with chylous ascites/chylothorax after extensive radical surgery for posterior mediastinum/retroperitoneum NB could be cured by non-surgical treatment. But the final result of original disease has not been greatly changed by

intensive surgery for stage 4 NB.

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Introduction

Chylothorax (ascites) is the accumulation of milk-like liquid which is rich in lymphocytes, triglycerides and chylomicrons in the thoracic (abdominal) cavity with a uniform, turbid and chylous-like appearance. Most of the chylothorax and chylous ascites are due to obstruction or rupture of lymphatic vessels.^[1] Posterior mediastinum and retroperitoneum are the most common sites of pediatric neuroblastoma (NB).^[2] The tumor often surrounds major retroperitoneal vessels and presents as infiltrative growth. These characteristics make surgery difficult, and increase the incidence of lymphatic vessels injury in the thorax or abdominal cavity, leading to chylothorax and/or chylous ascites.^[3] Reports of this complication in children are rare^[4] and its pediatric management is still under exploration. This study was undertaken to assess the efficacy of our experience in the management of postoperative chylous leakage, and evaluate the survivals of a group of NB patients especially at stage 4.

Methods

Patients

From May 2004 to January 2009, a total of 146 newly diagnosed NB children were treated at our hospital and 128 of them underwent surgery before or after chemotherapy. Of them, 12 children had their delayed extensive radical surgery which lasted longer than 10 hours; 11 of the 12 children had their surgery at other hospitals by parents' decision and another one had surgery at our hospital. Five in total, 4 boys and 1 girl, suffered from postoperative chylothorax and/or chylous ascites, four in stage 4 and one in stage

Author Affiliations: Department of Hematology/Oncology, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, 1678 Dongfang Road, Shanghai, China (Liu Y, Pan C, Tang JY, Chen J, Zhou M, Ye QD)

Corresponding Author: Jing-Yan Tang, MD, Department of Hematology/Oncology, Shanghai Children's Medical Center, 1678 Dongfang Road, 200127, Shanghai, China (Tel: +86-21-38626161-6061; Fax: +86-21-58756539; Email: yantfk@gmail.com)

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1-2. Their age at presentation ranged from 7 to 85 months (median: 19 months). One of the 5 children received posterior mediastinal radical tumor resection, 2 received retroperitoneal radical tumor surgery, and 2 received posterior mediastinal and retroperitoneal combined radical tumor resection. One patient of stage 1-2 had chylothorax on the third day after posterior mediastinal surgery in our hospital. Four patients of stage 4 had longer than 10 hours surgery, and developed chylothorax and/or chylous ascites immediately after surgery and returned to our hospital on day 7 after surgery. Their imaging examination showed a great amount of chest and/or abdominal effusion. Paracentesis and drainage were done immediately and fluid was diagnosed as chylous leakage. All of the 5 children identified here achieved very good partial remission (VGPR, residual tumor <10%, Fig.) after surgery. Their clinical characteristics are presented in the Table.

Our studies (therapeutic and diagnostic) were

approved by the Institutional Ethnic Board of Shanghai Children's Medical Center (SCMC). The surgical decisions were made by a tumor board including pediatric oncologists, surgeons, radiologists, and pathologists at SCMC with a written consent from the parents or guardians of the children.

Surgical procedures

The tumor diagnosed by medical imaging such as CT or MRI underwent initial resection before chemotherapy. Patients with NB of stages 3 to 4 at diagnosis with initially unresectable tumors were treated with induction chemotherapy with cisplatin, doxorubicin, etoposide, and cyclophosphamide for 3-6 cycles at 21-28 days intervals and then evaluated for treatment response which determined whether radical tumor resection would be given or not. Patients without disease progression underwent delayed resection of the primary tumor and bulky metastatic lesions that could

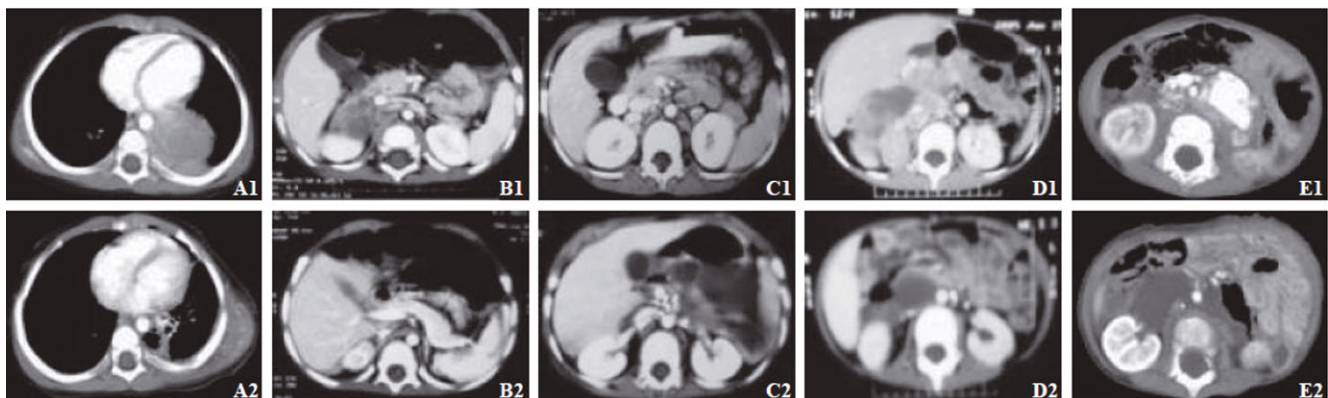


Fig. CT scan (contrast) of 5 neuroblastoma patients with chylothorax/chylous ascites before (A1, B1, C1, D1 and E1) and after surgery (A2, B2, C2, D2 and E2).

Table. Diagnosis and treatment of the 5 patients with chylous ascites/chylothorax following radical surgery of neuroblastoma

No.	Sex	Age (mon)	Staging at diagnosis	Infiltration site	Name of surgery	Duration of surgery (h)	Type of chylous leakage	Outcome of chylous leakage	Chylous leakage duration (d)	Total volume of drainage (mL)	Follow-up time (mon)	Patient status
1	M	19	NB-1-2	Left post mediastinum	Posterior mediastinum tumor gross total resection	2.5	Chylothorax	Cured	6	300	15	VGPR
2	M	85	NB-4	Right post mediastinum and retroperitoneum, BM	Retroperitoneal tumor gross total resection	17	Chylothorax & chylous ascites	Cured	32	18750	37	Relapse
3	F	52	NB-4	Post mediastinum and retroperitoneum, BM	Retroperitoneal + posterior mediastinum tumor gross total resection	13	Chylothorax & chylous ascites	Cured	33	2794	32	Relapse
4	M	7	NB-4	Right retroperitoneum, BM, bone	Retroperitoneal tumor gross total resection	11	Chylous ascites	Cured	30	9176	9	Relapse
5	M	13	NB-4	Post mediastinum and retroperitoneum, BM	Retroperitoneal + posterior mediastinum tumor resection (majority)	13	Chylous ascites	Cured	45	30715	14	VGPR

Case 1 had gross total resection by the surgeons but post-operation CT scan showed residual tumor. Case 5 did not respond to conservative treatment and was finally cured by surgery. All five children received gross total resection but had residual tumor shown by post-operation radiology. M: male; F: female; NB: neuroblastoma; BM: bone marrow; VGPR: very good partial remission.

be resected. The operative goal was total resection of the tumor including involved adrenal glands, sympathetic ganglia, and regional lymph nodes, without removal or permanent damage to other structures.

The operating surgeon assessed the extent of surgical resection during the operation and a radiologist compared both pre- and post-operative images to define postoperative status of the patient as complete resection, no visible tumor, VGPR (minimal residual, visible tumor less than 10%), partial resection (greater than 50% removal), and biopsy only.

Myeloablative chemotherapy followed by infusion of immunomagnetically purged autologous peripheral blood stem cell was applied to some stage 3-4 patients. And then all stage 3-4 patients were assigned to receive 13-cis retinoid acid 160 mg/m² per day after the ending of chemotherapy, 14 days per month for a total of 6 months.

Principles of conservative treatment for postoperative chylous leakage in our hospital

The basic principles of conservative treatment are the same for each patient. First of all, non-surgical comprehensive treatment was carried out, including diet control (fasting or non-fat/low fat diet), chest and/or abdominal cavity drainage and total parenteral nutrition (TPN). Hot nitrogen, glycolipids and electrolytes in the TPN formula were prescribed by nutrition physicians according to the patient's body weight, clinical symptoms, volumes of chest and/or abdominal fluid, and blood biochemical parameters. Basically, TPN included 20% lipofundin 1-2 g/kg per day, 6% amino acid 1-3 g/kg per day, soluvit 1 mL/kg per day, vitalipid 1 mL/kg per day, addamel 1 mL/kg per day, glycophos 1 mL/kg per day, and 40 kcal/kg per day (10 years old) to 80 kcal/kg per day (1 year old). At the same time, water and electrolyte balance was also maintained. When chest and/or abdominal effusion reduced to less than 50 mL per day, low-fat high-protein internal nutrition was given with medium to long chain fatty acid formula milk. Chylothorax and/or chylous ascites was considered to be clinically cured and the drainage tube could be removed if imaging examination showed that effusion disappeared 48 hours after clamping the drainage tube of the thoracic (abdominal) cavity. Whenever the patient had fever during the treatment of chylothorax and/or chylous ascites, aggressive measures such as bacterial culture of the drainage fluid should be carried out to search for possible infection sources, and then empiric or targeted antibiotic therapy was given according to the culture results. Managements for this group of patients were similar according to the principles without differences in relation to the primary site of tumor.

Imaging was not performed to locate the site of

lymphatic leakage in any of the patients. Somatostatin analogue was also not included in our principles. Surgical management of chylous leakage was recommended for children in whom conservative management with TPN failed after an interval of 4-8 weeks.

Results

Total volume, duration and outcome of chylothorax and/or chylous ascites

Chylothorax and/or chylous ascites lasted for 32, 33, 30 and more than 40 days respectively for four patients in stage 4. The patient in stages 1-2 also had chylothorax in 2.5 hours after surgery, but it only lasted 6 days and was cured after conservative management. The amount of leakage was 50-740 mL per day (median 285 mL).

Four of the 5 patients (3 in stage 4 and 1 in stages 1-2) were cured 6 to 32 days after conservative treatment. The other one who still had abdominal chylous-like fluid drainage of 600-700 mL/d (body weight 11 kg) was in poor general condition after 43 days of non-surgical treatment. He was considered to have no response to conservative management but recovered from abdominal chylous fistula repair by open surgery on day 45 (Table).

Continuous treatment after surgery and survival analysis

Three of the four patients in stage 4 received four courses of regular dosage chemotherapy continuously after the operation according to our protocol. The chemotherapy was given in 2 weeks after surgery even chylous ascites remained. Another stage 4 patient received 60% original dosage of chemotherapy for 2 courses and then the treatment was ceased because of poor general conditions of chylous ascites. Two patients of stage 4 NB were given autologous peripheral blood stem cell transplantation at the end of chemotherapy. All the stage 4 patients were given 13-cis retinoic acid after the end of chemotherapy at a dose of 160 mg/m² per day, 14 days per month for a total of 6 months. The other patient in stage 1-2 was found to have possibly a residual tumor by pathology and postoperative imaging examination. He received 6 courses of chemotherapy after surgery. All the 5 patients did not receive local radiotherapy.

Follow-up of the patients ranged from 9 to 37 months (median 15). Three of the 4 patients in stage 4 relapsed at 9, 32, and 33 months respectively since the beginning of chemotherapy. Among them, 2 patients had recurrence of primary site and 1 had bone marrow relapse. Only one patient in stage 4 who was diagnosed at the age of 13 months is still in disease progress free (DPF) after 14 months of follow-up. One patient of stage 1-2 is also in DPF 15 months after the diagnosis of NB (Table).

Discussion

Iatrogenic chylothorax and/or chylous ascites mainly occurs during the surgery when lymphatic vessels were damaged by accidental injury or perforation, which makes up approximately 30% of overall incidence.^[1] In this study, 4 (33%) of 12 NB patients who had received extensive radical tumor resection lasting for more than 10 hours were complicated with chylothorax and/or chylous ascites. This indicates that extensive radical surgery could lead to a higher incidence of chylous leakage. To reduce the possibility of postoperative chylous leakage, careful preoperative evaluation and less extensive surgery are necessary to avoid injury of lymphatic vessels from surgery.

Management scheme of chylous leakage includes strict fasting in early phase which is the first step to reduce the formation of chylous fluid and to lower the pressure in the lumen of the ruptured thoracic duct in order to promote its healing. Thoracic (abdominal) drainage is also given to alleviate the symptoms of dyspnea and/or abdominal distention due to massive pleural effusion and/or ascites. At the same time, appropriate formulations of TPN must be considered. Approximately, 66%-77% of the patients^[5,6] respond to conservative management after a 6-8 week period. About one third of the patients need operative intervention for failure of conservative management. Surgical options include primary direct surgical repair, fibrin glue application,^[7] embolization or creation of a peritoneovenous shunt.^[5,8] However, the exact duration that conservative therapy should be tried before surgical treatment is controversial.^[5,6,9] A period of 4-8 weeks is recommended,^[10-13] but early ligation or suturing of the leakage site may be helpful to avoid metabolic complications and prolonged hospitalization.^[14]

In our group, 4 of the 5 patients were cured after conservative treatment. We found that the prognosis of surgery for chylothorax and/or chylous ascites was generally good even though the healing time of lymphatic vessels was different in each patient. But for the patient who had abdominal chylous-like fluid drainage of 600-700 mL/d (body weight 11 kg) and was in poor general condition after 43 days of non-surgical treatment, chylous fistula repair was performed on day 45 instead of waiting for 8 weeks.

In patients with stage 3 and 4 NB, the primary tumor usually was large and locally invasive. Chemotherapy alone was unlikely to eradicate such disease. Surgery for these large and invasive tumors is technically challenging. All past and current clinical trials for NB patients have incorporated surgical resection of the primary disease site. In low-risk disease, the efficacy of surgical therapy is well established,^[15-19] however, the benefits of complete resection in high-risk patients,

especially on current intensive multimodality treatment protocols are not clear. Extensive radical surgery with severe injury which was also called "vascular skeletonum tumor total resection" would reduce tumor burden maximally so that very good partial remission or even no residual disease on diagnostic imaging can be achieved. A report from the Children's Cancer Group (CCG) study^[3] demonstrates a trend toward improved survival for those patients who had a complete resection. But there are also reports^[20-22] which did not fully support that result. In our study, all the 4 patients with stage 4 NB received similar surgical procedures lasting as long as 17, 13, 11, 13 hours respectively, of course, with severe injuries. Although postoperative imaging showed only a little or no evidence of residual disease, still 3 patients relapsed. This finding is in contrast to CCG reports even though the number of samples was small. Therefore, it is still debatable whether it is worthy to challenge the difficult-to-access NB for complete resection.

In short, chylous ascites after extensive radical surgery for NB can be treated conservatively in a majority of patients through diet control, drainage and appropriate formulations of TPN. Therefore, conservative treatment can be used as the preferred approach for the treatment of complications. If the patient does not respond to the above treatment and his or her general conditions are deteriorated after more than 4 weeks, surgical procedure should be considered.

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Contributors: Liu Y and Pan C co-wrote the paper and developed the assay with Zhou M and Ye QD. Chen J and Tang JY initiated the project, provided data, revised the paper and assisted with writing. All authors read and approved the final manuscript.

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