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The Management of Delayed-Onset Chylous Fistula after Neuroblastoma Resection in Children

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Abstract

Objective: Postoperative Chylous Fistula (CF) complicates neuroblastoma resection, extends hospitalization and delays adjuvant chemotherapy. We aimed to review our group of delayed-onset CF patients who underwent conservative treatment with tube drainage.

Methods: A retrospective study was conducted from our centre's neuroblastoma database. Patients who developed delayed-onset CF treated with tube drainage on or after POD 21 were included. Patients' demographic and clinical data were analyzed.

Results: Among 233 neuroblastoma resections performed over an 8-year period, 12 (5.2%) patients developed delayed-onset CF. They included stage 4 high-risk (n=11) and intermediate-risk (n=1) groups. They received 1-3 cycles of postoperative chemotherapy before CF was diagnosed. Percutaneous tube drainage of CF was performed on median POD 35 (21-126) that obtained mean of 1572 (600-4000) ml/day or 100 (27-186) ml/kg/day on day 1, followed by continuous drainage with conservative CF treatment, including medium-chain triglyceride diet, parenteral nutrition, octreotide and albumin infusion when indicated. Concurrent chemotherapy was administered in 8 patients based on neuroblastoma protocol without dose or schedule modification. Drainage tubes dwelled for median 33 (9-49) days, and CF resolved on median POD 66 (36-154) after neuroblastoma resection. Four patients with refractory CF also underwent successful surgical ligation. 5-year-EFS and OS for high-risk group were 70% and 90% respectively.

Conclusion: Conservative treatment with tube drainage remains the first-line approach to postoperative CF. Concurrent chemotherapy may proceed without dose modification. Adequate adherence to chemotherapy protocol ensures comparable oncological outcome.

Keywords: Chylous fistula; Neuroblastoma; Surgery

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Introduction

Chylous Fistula (CF) is a rare complication in pediatric oncological surgery [1]. Nevertheless, it has been reported more often in neuroblastoma, with few related to lymphadenectomies in Wilms tumor [2]. Its predominance in neuroblastoma is likely related to the abundance of abnormally dilated lymphatic channels, called megalymphatics, secondary to retroperitoneal tumor obstruction [3]. As such, iatrogenic disruption of megalymphatics is often unavoidable in neuroblastoma resection.

CF results in significant morbidity. The loss of chyle, which is rich in proteins, lipids, lymphocytes, immunoglobulins, electrolytes, and vitamins, has been known to result in nutritional and electrolyte deficiencies, and immunosuppression [4,5]. These complications extend hospitalization, delay or preclude adjuvant chemotherapy and may adversely affect oncological outcome [6].

Publications have shown the efficacy of conservative nonsurgical treatment without compromising oncological treatment in early-onset CFs detected at primary surgical drains [6,7]. When refractory cases were encountered, surgical ligation [8], application of fibrin glue [9], peritoneovenous shunt [10] and lymphatic embolization [11] have been reported with success. Despite the above, we have adopted a conservative-first approach with percutaneous continuous drainage while permitting the administration of chemotherapy according to the treatment protocol for neuroblastoma.

We identified and analyzed a subset of patients who developed delayed-onset CF following a CF-free postoperative period while on chemotherapy. We aimed to illustrate their clinical presentations, the effects of large-volume paracentesis and the implications on the oncological treatment.

Methods

We retrospectively reviewed our centre's neuroblastoma database and identified patients who were diagnosed with delayed-onset CF after neuroblastoma resection from August 2013 to July 2021. Only patients who developed symptoms of CF, such as gross abdominal distension from ascites associated with impairment of pulmonary, renal, and gastro-intestinal function, and respiratory distress from pleural effusion, and had received secondary tube drainage on or after postoperative day 21 (≥ POD 21) were included. Patients' demographic data and clinical course were reviewed and analyzed. Patients were staged and risk-stratified according to the INSS (International Neuroblastoma Staging System) and COG (Children's Oncology Group) risk categories. Low-risk patients underwent upfront resection whenever feasible while Intermediate-Risk (IR) and High-Risk (HR) groups underwent complete resection of primary tumour and involved lymph nodes after neoadjuvant chemotherapy.

Patients diagnosed with CF before POD 21 were excluded. These patients were usually diagnosed in the early postoperative period as a result of routine placement of primary surgical drains at all neuroblastoma resections. While they were managed according to our centre's postoperative CF protocol, we believe some of them were asymptomatic low-volume CF that would have self-limited without treatment if not for the primary surgical drain in-situ.

Similarly, patients with delayed-onset CF would have also received routine placement of primary surgical drains at surgery that were removed once they were deemed CF-free. Adjuvant chemotherapy would then be administered according to the chemotherapy protocol. Patients who subsequently developed symptoms of CF underwent image-guided (ultrasonography or CT) percutaneous placement of secondary drainage tube. The alternative option of needle aspiration was not considered as it would have only provided temporary symptomatic improvement with recurrence of distress needing repeated aspirations. Close monitoring after the procedure with hourly blood pressure, continuous heart rate and oxygen saturation measurements for at least 6 h was mandatory. While on an indwelling drainage tube, they continued with adjuvant chemotherapy according to protocol without dose or schedule modification, together with various combinations of Medium-Chain Triglyceride (MCT) diet, parenteral nutrition and octreotide until resolution. Prophylactic antibiotic was not routinely given for the presence of drainage tube. Outpatient management was permitted in patients with abdominal drains in-situ who were able to maintain adequate oral intake and were willing to return for twice-weekly blood tests and albumin infusion as necessary. Decisions for surgical ligation of CF were made when timely resolution before Autologous Stem Cell Transplantation (ASCT) or immunotherapy was deemed unlikely. Its surgical technique has been described previously [8].

Results

Among 233 patients who underwent surgical resection of neuroblastoma in the above period, 12 (5.2%) developed delayed-onset CF ≥ POD 21. The latter's average age was 4.2 (0.9-10.5) years, average body weight 15.6 (8-26.3) kg with male-to-female ratio 7:5. Eleven patients were stratified as stage 4 HR group and 1 was stage 4 IR group. MYCN amplification was present in 3 patients. Their primary tumors were located in the abdomen (n=9) and thoraco-abdomen (n=3). All received neoadjuvant chemotherapy before neuroblastoma resection.

After adequate recovery from neuroblastoma resection, the patients commenced adjuvant chemotherapy on median 14 (11-24) POD. While 8 of them became symptomatic after 1 cycle of chemotherapy, 3 patients received 2 cycles and 1 patient received 3 cycles before symptoms. Two patients also underwent peripheral stem cell harvest prior to symptoms. Their clinical manifestations were gross ascites with significant abdominal distension (n=11) and respiratory distress with pleural effusion (n=1) before they underwent secondary tube drainage on median 35 (21-126) POD.

Among 11 patients with abdominal chylous ascites, 1 developed recurrence of CF that required drainage, making up 12 episodes of secondary abdominal tube paracentesis for analysis. Eight patients with abdominal tube in-situ were managed as outpatients, of which 5 were discharged from the hospital after 6 h of observation, 2 were observed overnight, 1 remained hospitalized for 8 days for chemotherapy, and 4 remained hospitalized for 7 to 26 (mean 16) days until complete resolution. There was only 1 patient with pleural chylous effusion. He had undergone single-stage resection of left thoraco-abdominal neuroblastoma. According to our centre's protocol for thoracic drains, he remained hospitalized throughout tube pleurocentesis for 38 days until complete resolution.

The patient who had recurrent chylous ascites was a 4-year-old boy whose chylous ascites was first drained on POD75 after neuroblastoma resection. His first CF resolved 37 days later, only to require another drainage tube 14 days later. Despite further 21 days of treatment, he underwent surgical ligation of refractory CF. During his protracted treatment for CF, he underwent 3 cycles of chemotherapy and a peripheral stem cell harvest. His surgical ligation was successful and he was able to complete his myeloablative chemotherapy with ASCT.

On the first day of secondary drainage procedure, the patients drained mean 1572 (600-4000) ml/day of chylous fluid, or 100 (27-186) ml/kg/day. All patients tolerated the drainage procedures well with hemodynamic stability without the need for fluid or inotropic resuscitation. Pre-drainage blood tests were routinely performed but paired blood investigations were only documented in 9 patients before and after drainage. Four patients were neutropenic, of which 1 also had pre-drainage hypokalemia and post-drainage hyponatremia that required replacement therapy. Seven patients developed hypoalbuminemia <30 g/L after drainage and received albumin infusion. After tube placement, inpatients underwent continuous drainage and were given parenteral nutrition with oral MCT diet. Three patients also received octreotide for mean 7 (3-9) days but without response. Outpatients were allowed to drain up to maximum of 400 ml/day while being maintained on oral MCT diet and twice-weekly albumin infusion if required.

Eight patients received chemotherapy without dose reduction while on indwelling drainage tube. The chemotherapy combinations included cisplatin-etoposide (PVP), Cyclophosphamide-Doxorubicin-Vincristine (CAV), Vincristine-Topotecan-Cyclophosphamide (VTC), Vincristine-Irinotecan-Temozolomide (VIT), and Ifosfamide-Carboplatin-Etoposide (ICE). Regimen modification was made only when neuroblastoma was refractory to

first-line treatment. Patients received 1 cycle (n=4), 2 cycles (n=1), and 1 cycle with stem cell harvest (n=2), whilst one even received myeloablative thiotepa-cyclophosphamide with ASCT. Four patients did not receive chemotherapy while on indwelling drainage tube for 9-21 (median 10.5) days as they were not due for chemotherapy. Only 1 patient developed drain infection with Acinetobacter baumannii that resulted in drain removal on day 18. The infection occurred when she was recovering from chemotherapy-related neutropenia. Her CF spontaneously resolved soon after drain removal.

Overall, the drainage tubes dwelled for median 33 (9-49) days, and CF resolved on median POD 66 (36-154) after neuroblastoma resection. Among 4 patients who underwent surgical ligation for refractory chylous ascites, they were performed on median POD 72 (44-154). Three patients underwent surgery (on POD 44, POD 65, POD 78 respectively) prior to myeloablative bulsufan-melphalan with ASCT and or immunotherapy, while 1 patient underwent surgery on POD 154 when he suffered second episode of chylous ascites. After successful surgical ligations, the drainage tubes were removed after median 5 (4-7) days.

All 11 HR patients were able to complete their treatments according to HR protocols, including ASCT (n=5), ASCT with immunotherapy (n=3), and immunotherapy (n=3), with 5-year event-free and overall survival 70% and 90% respectively, and median follow-up of 4.5 (1.8-8.1) years. The only patient with stage 4 IR has remained well and disease-free for 6.3 years.

Discussion

CF remains a challenge in neuroblastoma resections. In spite of preventive measures such as prophylactic mesenteric lymphatic ligation, delayed commencement of postoperative feeding, and negative "fat challenge test" before surgical drain removal, we found our patients with delayed-onset CF an intriguing subset [8]. As these patients had proceeded to receive postoperative chemotherapy promptly prior to developing CF, we suspect that the associated hyperhydration therapy and cytotoxicity were possible contributing factors. An increase in chylous drainage was consistently observed at chemotherapy and peripheral stem cell harvest. We postulated that hyperhydration may have led to lymphatic hypervolemia while cytotoxicity may slow healing of the injured lymphatics. Even though delaying the recommencement of postoperative chemotherapy may be an attractive option, we avoided this stance for fear of subsequent tumor recurrence and treatment failure.

Percutaneous drainage of gross ascites and massive pleural effusion provided quick symptomatic relief. Similar to previous reports on massive ascites, we found large-volume paracentesis to be safe if closely monitored. Characteristic hemodynamic changes following paracentesis that resulted in an exponential drop in abdominal pressure consisted of decrease in right atrial and pulmonary pressures, decrease in mean arterial pressure, increase in cardiac output and systemic vasodilatation. In response to vasodilatation, activation of the renin-angiotensin and sympathetic nervous system would occur [12]. Our young patients would usually be able to compensate for the vasodilatation to maintain circulatory homeostasis. Unlike paracentesis, pleurocentesis for massive pleural effusion should be gradual and controlled to avoid life-threatening re-expansion pulmonary edema.

Daily loss of chyle has been commonly associated with nutritional deficiencies [4]. The loss of lipid and protein was most obvious in our patients, further aggravated by dietary modifications and noncompliance. The latter was a common childhood misbehavior and usually worsen by chemotherapy-related anorexia. Enteral and intravenous supplements were routinely prescribed in protracted refractory CF. Early hypoalbuminemia was a common finding in chylous drainage and would persist unless infused with albumin. We have routinely kept our patients' serum albumin above 30 g/L to maintain systemic oncotic pressure. Electrolyte deficiency was not encountered in our cohort, except in a patient who had concurrent renal impairment. It has often been postulated that patients with CF may suffer from immunosuppression due to the loss of immunoglobulins and lymphocytes [5]. We had not measured serum immunoglobulin levels in our patients and chemotherapy-related fluctuation in blood lymphocyte count would have affected its interpretation. Nevertheless, our patients did not experience manifestation of immunosuppression that was atypical in children on chemotherapy.

Chemotherapy has been known to be associated with acute systemic effects. An additional drainage tube in-situ coupled with continuous chylous drainage during a period of immunosuppression may predispose to life-threatening sepsis. Close clinical monitoring of our patients did not reveal any adverse effects but periodic supplementary parenteral nutritional seemed beneficial. Even though prophylactic antibiotic for the drain was not given, only 1 patient developed drain infection that resolved with drain removal and a course of therapeutic antibiotics.

Octreotide, a somatostatin analogue, has been shown to quicken recovery and significantly shorten hospital stay in CF [6]. Its efficacy may be a result of its ability to reduce gastric, pancreatic, and intestinal secretions, to inhibit intestinal motor activity, and to slow intestinal absorption, reducing splanchnic blood flow and decreasing hepatic venous pressure. Our experience, however, showed the results in octreotide to be unpredictable, and a standard regime defining its optimal dosage and duration for optimal action is still lacking. Its high cost has also deterred us from its routine usage.

Invasive methods of CF management have been described. Peritoneovenous shunt has been reported with success [10], whereas others noted a high failure rate associated with complications such as shunt fracture or occlusion. Recent reports on intranodal lymphangiography and lymphatic embolization for management of iatrogenic chylous ascites in children have shown optimism [11]. Lymphangiography alone has reduced lymphatic leaks as lipiodol, an ethiodized oil contrast agent, may induce an inflammatory and granulomatous reaction on the extravasation to seal the leakage [13]. However, the results have not been consistent.

We performed surgical ligation in 4 patients that promptly resolved the CF, removing the drainage tube in 5 days. There is yet a standard recommendation on the maximum period of conservative treatment before which invasive or surgical treatments should be considered [14]. In our patients, surgical ligation was aimed at arresting CF before patients underwent myeloablative chemotherapy-ASCT and/or immunotherapy. Despite our concerns, we successfully completed ASCT with thiotepa-cyclophosphamide regime while concurrently managing the child's tube drainage of CF.

We acknowledge the limitations of such a retrospective study of an uncommon condition. Besides the small number of patients, they manifested at various time-points in their postoperative period.

The decision to perform surgical ligation was also influenced by our experience and parental preference and consent.

In conclusion, conservative treatment with tube drainage remains the first-line approach to postoperative CF. Concurrent chemotherapy may proceed without dose or schedule modification. In refractory cases, definitive surgical ligation planned around the chemotherapy schedule is a feasible option. Adequate adherence to chemotherapy protocol ensures comparable oncological outcome.

References

1. Ardicli B, User IR, Ciftci AO, Karnak I, Tanyel FC, Ekinci S. An unusual complication of tumor surgery: Chylous leakage. Surg Today. 2021.
2. Weiser AC, Lindgren BW, Ritchey ML, Franco I. Chylous ascites following surgical treatment for wilms tumor. J Urol. 2003;170(4):1667-9; discussion 1669.
3. Bhardwaj R, Vaziri H, Gautam A, Ballesteros E, Karimeddini D, Wu GY. Chylous ascites: A review of pathogenesis, diagnosis and treatment. J Clin Transl Hepatol. 2018;6(1):105-13.
4. Gaglio PJ, Leevy CB, Koneru B. Peri-operative chylous ascites. J Med. 1996;27(5-6):369-76.
5. Camiel MR, Benninghoff DL, Alexander LL. Lymphocytopenia with lymph extravasation from abnormal lymphatics: Its occurrence with chylous ascites and chylothorax. Lymphology. 1970;3(4):147-51.
6. Pio L, Boccardo F, Avanzini S, Paraboschi I, Granata C, Garaventa A, et al. Conservative management of chylous ascites after oncological surgery for X peripheral neuroblastic tumors in pediatric patients. Lymphology. 2019;52(1):25-34.
7. Qureshi SS, Rent EG, Bhagat M, Dsouza P, Kembhavi S, Vora T, et al. Chyle leak following surgery for abdominal neuroblastoma. J Pediatr Surg. 2016;51(9):1557-60.
8. Chui CH. Mesenteric lymphatic ligation in the prevention of chylous fistulae in abdominal neuroblastoma surgery. Pediatr Surg Int. 2014;30(10):1009-12.
9. Zeidan S, Delarue A, Rome A, Roquelaure B. Fibrin glue application in the management of refractory chylous ascites in children. J Pediatr Gastroenterol Nutr. 2008;46(4):478-81.
10. Matsufuji H, Nishio T, Hosoya R. Successful treatment for intractable chylous ascites in a child using a peritoneovenous shunt. Pediatr Surg Int. 2006;22(5):471-3.
11. Moussa AM, Maybody M, Santos E, Gonzalez-Aguirre AJ. Intranodal lymphangiography and lymphatic embolization for management of iatrogenic chylous ascites in children. Lymphat Res Biol. 2021.
12. Sola-Vera J, Such J. Understanding the mechanisms of paracentesis-induced crculatory dysfunction. Eur J Gastroenterol Hepatol. 2004;16(3):295-8.
13. Becker J, Pavlakovic H, Ludewig F, Wilting F, Weich HA, Albuquerque R, et al. Neuroblastoma progression correlates with down regulation of the lymphangiogenesis inhibitor sVEGFR-2. Clin Cancer Res. 2010;16(5):1431-41.
14. Lee EW, Shin JH, Ko HK, Park J, Kim SH, Sung KB. Lymphangiography to treat postoperative lymphatic leakage: A technical review. Korean J Radiol. 2014;15(6):724-32.