Research Article

Hypoalbuminemia Associated with Neuroblastoma: A Single Institution Experience

Pournima Navalkele[1], Kevin Belgrave[1], Deniz Altinok[2], Kanta Bhambhani[1], Jeffrey W. Taub[1] and Zhihong J. Wang[1]*

[1]Division of Pediatric Hematology Oncology, The Carman and Ann Adams Department of Pediatrics, Wayne State University, USA
[2]Department of Radiology, Children's Hospital of Michigan, Wayne State University, USA

Copyright

Abstract

Hypoalbuminemia is common in the intensive care setting, and preoperative hypoalbuminemia is reported to be associated with an increased risk of post-operative complications in adult cancer patients. However, studies of hypoalbuminemia in childhood cancers are scarce.

Objective: We conducted a study to look at the incidence of hypoalbuminemia at diagnosis of neuroblastoma, the most common extra-cranial solid cancer in children.

Study design: We performed a retrospective chart review of the neuroblastoma cases diagnosed between 2007 and 2013 at our institution.

Results: Among the 30 cases with serum albumin levels available at diagnosis, the albumin level was <3.5 g/dL in 16 cases (53%), <3 g/dL in 10 cases (33%), and <2 g/dL in 4 cases (13%). While hypoalbuminemia was multifactorial, we believe that protein-losing-enteropathy, likely due to tumor-related enteric lymphatic obstruction and lymphangiectasia, was one of the causes.

Conclusion: Hypoalbuminemia was a frequent finding in our cohort, and further investigation in a larger study is warranted.

ABBREVIATIONS

CHM: Children's Hospital of Michigan; ALC: Absolute Lymphocyte Count; PT: Prothrombin Time; α1-AT: α1-antitrypsin; PLE: Protein-Losing-Enteropathy

INTRODUCTION

Hypoalbuminemia is common in the intensive care setting, and serum albumin levels have been reported to be of prognostic value in children with sepsis [1]. In addition, preoperative hypoalbuminemia has been linked to increased post-operative complications in adult cancers [2,3]. Studies of hypoalbuminemia in childhood cancers, however, are scarce [4], and the incidence of hypoalbuminemia at diagnosis of neuroblastoma, the most common extra-cranial solid tumor in children. In order to gain insight into the incidence of hypoalbuminemia and its causes in neuroblastoma, we conducted a retrospective review of our patients with hypoalbuminemia in neuroblastoma.

METHODS

This project was approved by Human Investigation Committee of Wayne State University. Thirty-five consecutive cases of neuroblastoma diagnosed and treated from 2007 to 2013 at Children's Hospital of Michigan (CHM) were identified from the institutional oncology database. Serum albumin levels at diagnosis were available in 30 cases.

RESULTS AND DISCUSSION

A total of 35 consecutive cases of neuroblastoma were reviewed of which 30 had albumin levels available at diagnosis. The age, gender, serum albumin level at the time of diagnosis, absolute lymphocyte count, tumor stage and location(s), risk group and N-MYC amplification are shown in Table (1). Sixteen patients (46%) were ≤ 1 year and 33 patients (94%) were ≤ 5 years of age. Twenty-four (69%) patients had abdominal (including adrenal, retroperitoneal ad pelvic locations) tumors.

SciMedCentral

Table 1: Demographic and clinical features of Neuroblastoma cases.

Patient	Age*	Sex	Albumin (g/dL)	ALC k/mm3	Tumor location(s)**	INSS stage#	N-myc amplification	Risk Group
1	14 m	F	4.9	600	Paraspinal (C+T), Retroperitoneum, BM	stage 4	No	High
2	10 d	M	2.8	2800	Adrenal, BM, liver	stage 4S	No	Low
3	9 y	F F	2.6	1600	Paraspinal (C), BM	stage 4	No	High
4	2y	M	3.3	3100	Pelvis, BM	stage 4	No	High
5	13 m	F	NA	6600	Paraspinal (T)	stage 2b	No	Low
6	3 m	F	1.8	5700	Adrenal, BM, liver	stage 4S	No	Intermediate
7	3 m	F	2.7	12900	BM, liver@	stage 4S	No	Intermediate
8	2 y	M	4	3900	Abdomen, BM	stage 4	No	High
9	20 m	F	4.8	4200	Paraspinal (T)	stage 2a	No	Low
10	1 m	F	3.6	5200	Paraspinal (L)	stage 3	No	Intermediate
11	4 y	M	3.5	4600	Abdomen, BM	stage 4	No	High
12	16 m	F	3.6	5400	Retroperitoneum, BM	stage 4	Yes	High
13	5 m	F	3.5	5500	Retroperitoneum, liver	stage 4S	Yes	Intermediate
14	18 m	F	**2.4**	**1200**	Retroperitoneum, BM, bone	stage 4	No	High
15	14 m	F	**3.3**	**2600**	Paraspinal (T)	stage 2b	NA	Intermediate
16	5 y	M	3.8	4400	Abdomen , BM	stage 4	No	High
17	10 m	M	NA	12800	Paraspinal (L)	stage 3	No	Intermediate
18	12 m	M	4.3	**3200**	Retroperitoneum	stage 3	No	Intermediate
19	11 m	F	3.8	13000	Retroperitoneum	stage 4	No	Intermediate
20	4 y	F	**2.6**	2400	Paraspinal (C), BM, bone	stage 4	No	High
21	17 m	F	NA	10400	Adrenal, BM	stage 4	Yes	High
22	9 d	M	**2.2**	**1900**	Adrenal, liver	stage 4S	No	Intermediate
23	5 y	M	**3.2**	3900	Adrenal	stage 3	No	High
24	10 m	M	4.5	11200	Abdomen	stage 3	No	Intermediate
25	16 d	M	**3.3**	5800	Paraspinal (C)	stage 3	No	Intermediate
26	10 m	F	**3.3**	4400	Abdomen, BM, bone	stage 4	Yes	High
27	19 m	F	3.8	4400	Adrenal, BM, bone	stage 4	No	High
28	11 m	F	**1.4**	**1500**	Abdomen, BM	stage 4	No	Intermediate
29	2 m	F	NA	2900	Paraspinal (T+L)	stage 2b	No	Low
30	2 y	F	3.7	4300	Paraspinal (T)	stage 2a	No	Low
31	11 d	F	NA	6200	Adrenal	stage 2a	No	Low
32	10 m	F	**0.9**	**900**	Abdomen, BM, bone	stage 4	No	Intermediate
33	3 y	M	**1.8**	**600**	Retroperitoneum	stage 3	No	High
34	3 y	M	**3.3**	2700	Adrenal	stage 1	No	Low
35	8 yr	F	3.7	1900	Adrenal	stage 2b	No	Low

*Age, d=days, m=months, y=years.**Tumor location: C=cervical, T=thoracic, L=lumbar, BM=bone marrow. #INSS: International Neuroblastoma Staging System.@Patient 7 was twin of patient 6, no primary tumor was found.

The age profile and predominance of abdominal tumors were similar to that reported in the literature [5]. There were 15 cases (43%) with stage 4, 5 cases (14%) with stage 4S, 7 cases (20%) with stage 3, 7 cases (20%) with stage 2, and 1 case (3%) with stage 1 disease. Interestingly, hypoalbuminemia was a frequent finding among patients with neuroblastoma at diagnosis in our cohort. Serum albumin level was < 3.5 g/dL in 16 cases (53%), < 3 g/dL in 10 cases (33%), and < 2 g/dL in 4 cases (13%). Among the 24 patients with abdominal tumors, serum albumin level was < 3.5 g/dL in 11 (46%) cases, < 3 g/dL in 7 (29%) cases, and < 2 g/dL in 4 (17%) cases. Of the 7 patients with abdominal tumor and albumin <3 g/dL, 5 patients (71%) had absolute lymphocyte count (ALC) below normal range for age. 4 patients with abdominal tumor and albumin <2 g/dL, 3 (75%) had low ALC. While the incidence of hypoalbuminemia (albumin <3.5 g/dl) in

patients with abdominal tumor was not increased compared to the entire cohort, four patients with severe hypoalbuminemia (albumin < 2 g/dL) all had abdominal tumors. One of these 4 patients was a 2-month-old infant with a stage 4S neuroblastoma with an adrenal primary tumor and diffusely enlarged liver due to metastasis with concurrent coagulopathy. Her albumin level at diagnosis was 1.8 g/dL, and decreased hepatic synthetic function was felt to be a major cause of her hypoalbuminemia. We reviewed the clinical courses of the other three patients and hoped it would shed light on the causes of hypoalbuminemia.

Case 1

A 10-month-old Caucasian female presented with lower extremity swelling and diarrhea, and refused to bear weight

on her legs. On admission, she was noted to have significant bilateral lower extremity edema and abdominal distension with a large palpablemass. The serum albumin level was 0.9 g/dL and urinalysis was negative for protein. Lymphopenia was noted with an ALC of 900 /mm^3, and prothrombin time (PT) was 10.1 seconds. The stool α1-antitrypsin (α1-AT) level was elevated; gliadin antibody was negative, and cow's milk IgE was not elevated. An abdominal MRI demonstrated a mass encasing and compressing the major abdominal vessels with marked thickening of the intestinal wall (Figure 1A & 1B). She received intravenous albumin infusion before undergoing a laparoscopic biopsy of the tumor and had an unremarkable post-operative course. The pathology was consistent with favorable histology neuroblastoma with no N-MYC amplification. The bone marrow had tumor infiltration and the bone scan showed diffuse osseous metastases, consistent with stage 4 intermediate risk neuroblastoma. She was treated using carboplatin, etoposide, cyclophosphamide and doxorubicin, and had a significant reduction of tumor in size and normalization of the intestinal wall following 2 cycles of chemotherapy (Figure 1C & 1D). The serum albumin level normalized without supplementation within a 4 months period. She underwent surgical resection of the residual tumor after 8 cycles of chemotherapy and received 6

cycles of maintenance therapy with isotretinoin. She is currently in remission, 11 months off therapy.

Case 2

An 11-month-old African-American female presented with swelling of lower legs and diarrhea. On examination, she was well nourished with mild bilateral lower leg edema, mild abdominal distension but without a palpable mass. The serum albumin was 1.4 g/dL, ALC was 1,500/ mm^3, and PT was 10.1 seconds. Urinalysis showed trace protein with a normal BUN and creatinine. A MRI of the abdomen demonstrated a large retroperitoneal mass with vascular encasement and compression, a markedly thickened bowel wall and the presence of cavernous transformation of the portal vein (Figure 2A & 2B). She underwent a laparotomy with biopsy of the abdominal tumor and pathology was consistent with unfavorable histology neuroblastoma with no N-MYC amplification. There was bone marrow involvement with tumor though the bone scan was normal, consistent with Stage 4 intermediate risk neuroblastoma. She had a complicated post-operative course with septic shock, disseminated intravascular coagulation, liver failure, renal failure required dialysis, and ischemic encephalopathy, and was on ventilator support for over a month. She received a total of 8 cycles of chemotherapy utilizing carboplatin, etoposide,
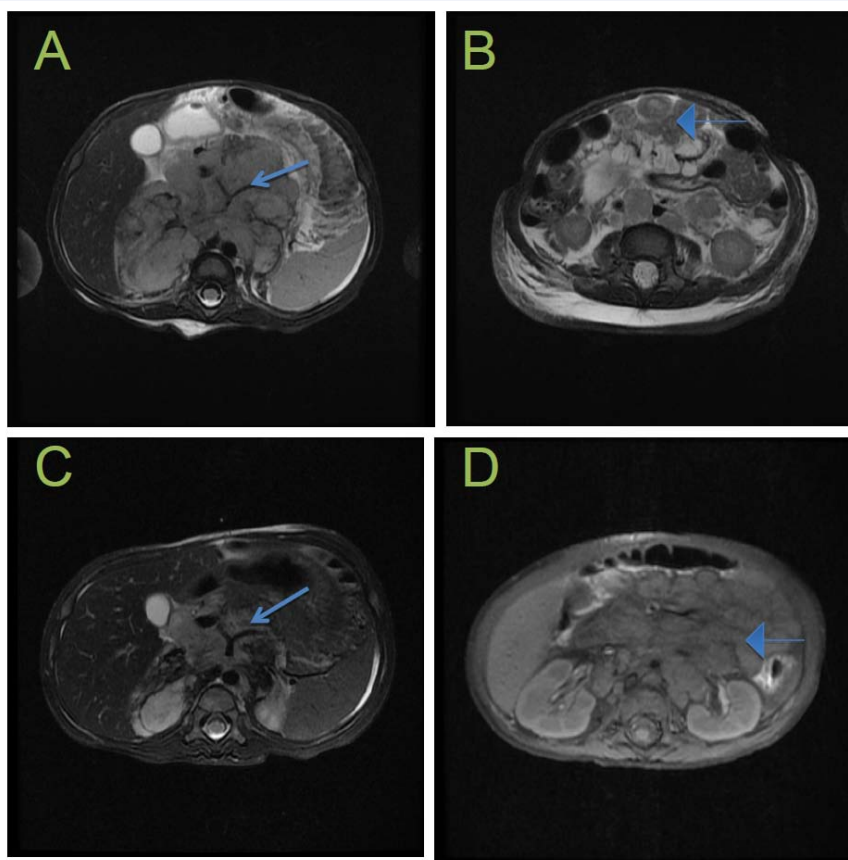

Figure 1 Case 1 MRI images.
A&B: Axial T2 image at diagnosis showed large lobulated solid retroperitoneal mass with significant encasement of celiac artery (A, open arrow) and bowel loops with thickened bowel wall (B, solid arrow). C&D: After 2 cycles of chemotherapy, significant reduction in size of the tumor with increased diameter of celiac artery (C, open arrow) and normal bowl loops (D, solid arrow) were observed.
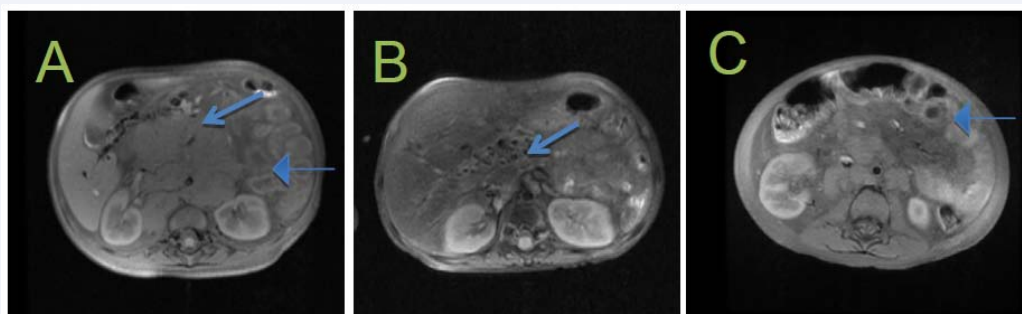
Wang et al. (2016)
Email: jwang2@med.wayne.edu

⏺SciMedCentral

Figure 2 Case 2 MRI images.
A&B: T1W axial image at diagnosis shows retroperitoneal, solid mass with celiac artery encasement (A, open arrow) and significantly thickened bowel wall in intestines (A, solid arrow) and cavernous transformation of the portal vein (B, open arrow). C: normal bowl loops following chemotherapy (solid arrow).

cyclophosphamide and doxorubicin, with a significant reduction of tumor in size before she underwent surgical resection of the residual tumor. The bowel wall thickening resolved on the MRI evaluation at three months after starting chemotherapy (Figure 2C) and albumin level normalized without supplementation. She is currently in remission, 35 months off therapy.

Case 3

A 3-year-old African-American male presented with a one-month history of progressive painless abdominal distention and bilateral lower extremity edema. On exam, there was significant pitting edema of his bilateral lower extremities. His abdomen was distended but no mass was palpated. His serum albumin was 1.8 g/dL, ALC was 600/ mm^3, PT was 10 seconds and urinalysis was negative for proteinuria. MRI of the abdomen demonstrated a mass in the right upper abdomen which encased the major abdominal vessels. He received intravenous albumin supplement before he underwent a laparotomy with biopsy of the abdominal tumor. The pathology was consistent with unfavorable histology neuroblastoma with no N-MYC amplification, and bone scan and bone marrow was negative for metastasis; the findings were consistent with stage 3, high risk neuroblastoma. After 2 cycles of chemotherapy with cyclophosphamide and topotecan, his leg edema resolved and albumin level normalized. He received additional 3 cycles of chemotherapy using cisplatin, etoposide, cyclophosphamide, doxorubicin and vincristine followed by subtotal resection of tumor, high dose chemotherapy with autologous stem cell rescue and radiation therapy. He received maintenance therapy with 1 cycle of anti-GD2 antibody and isotretinoin before the treatment was discontinued per family's request. He iscurrently in remission, 12 months off therapy.

The initial symptoms of neuroblastoma are frequently non-specific and may mimic a wide variety of common pediatric conditions, due to the numerous possible sites of involvement of both the primary tumor and metastases. In addition, some symptoms can be attributed to the associated metabolic disturbance adding to the difficulty in early detection of the tumor [6]. In our cohort, hypoalbuminemia was a frequent finding at diagnosis of neuroblastoma, and serum albumin levels <3.5 gram/dL was present in 53% of patients. Therefore, hypoalbuminemia without a known etiology could be another

red flag for neuroblastoma in infants and young children, since 40% of patients with neuroblastoma are diagnosed in infancy, and 90% by 5 years of age [5]. By considering this diagnosis, pediatricians can readily make the referral, or order imaging studies, to aid in the prompt detection of this malignancy.

The etiology of hypoalbuminemia can be due to several different factors including decreased production due to protein malnutrition (Kwashiorkor) and defective synthesis (liver diseases), increased loss due to protein-losing enteropathy (PLE), nephrotic syndrome or excessive burns, or redistribution due to inflammation of capillaries (sepsis) or hemodilution. PLE is believed to be a rare condition characterized by protein loss through the gastrointestinal tract, as the mucosa lining the gastro-intestinal tract fails to hold back the proteins of tissue fluids, leading to reduced serum protein levels [7,8]. Proteins are primarily absorbed in the small bowel, and any condition that affects the digestion or absorption of protein can result in PLE. The most affected protein is albumin because of its slow turnover rate in steady state; therefore hypoproteinemia in PLE is usually detected as hypoalbuminemia.

PLE can be broadly categorized into conditions which cause inflammation of gastrointestinal tract (infectious gastroenteritis, milk-protein allergy, inflammatory bowel disease, celiac disease and malnutrition), enteric lymphatic obstruction (intestinal lymphangiectasia, whipple disease, malrotation, volvulus, retroperitoneal tumor, bowel infiltration from leukemia or other malignancies) and increased systemic venous pressure (cardiomyopathy, post Fontan operation, congestive cardiac failure). There are two different mechanisms through which an increase in intestinal plasma protein loss, or PLE, can occur: (1) abnormalities of the lymphatic system, resulting in leakage of protein-rich lymph and (2) mucosal injury, with increased mucosal permeability. Fecal α1-AT is a sensitive endogenous marker of gastrointestinal protein loss [7,8].

While hypoalbuminemia in neuroblastoma could be multifactorial, we felt that PLE was likely one of the causes in the three cases we describe. There was no evidence of increased protein loss from the kidney, and normal prothrombin time suggesting a normal hepatic synthetic function in all 3 cases. A review of the literature revealed 5 previously reported cases

Wang et al. (2016)
Email: jwang2@med.wayne.edu

◉SciMed Central

associating neuroblastoma with PLE [6, 9-12]. In one of these cases, PLE was attributed to neurohumoral mechanisms of catecholamines secreted by neuroblastoma cells [10]. It is well described that Vasoactive Intestinal Polypetide (VIP) secreted by neuroblastoma (VIPoma) causes voluminous watery diarrhea [13,14]. In the other cases, intestinal lymphangiectasia due to lymphatic obstruction by the tumor was reported [6,9,11]. In one of the cases, CT imaging revealed diffuse bowel wall thickening suggestive of lymphatic obstruction, and flow of what appeared to be chylous material was observed during the tumor biopsy [9]. In another case, duodenal biopsy was performed which showed the presence of abnormally dilated lymphatic vessels suggestive of lymphangiectasia, which was further confirmed on autopsy [6]. PLE has been described in other malignant neoplasms, such as leukemia, lymphoma, gastrointestinal carcinomas and colon cancer [11,12,15-18]. The proposed mechanisms for the occurrence of PLE in malignancy include protein loss through the inflamed or ulcerated mucosa, such as in gastrointestinal carcinomas, direct tumor infiltration such as in lymphoma, lymphatic obstruction from tumor compression, and chronically elevated right-sided venous pressure from carcinoid syndrome.

In our three cases, enteric lymphatic obstruction and intestinal lymphangiectasia, secondary to the mass effect of the tumor and increased venous pressure from tumor compressing the vasculature, was likely the etiology of PLE. In addition to the very low albumin levels, all three patients were lymphopenic, which is a common finding in intestinal lymphangiectasia due to the intestinal loss of lymphocytes, and elevated stool α1-AT level in the first case further supported the diagnosis of PLE. MRI images at diagnosis showed significant bowel wall thickening, also suggesting the presence of lymphatic obstruction.

CONCLUSION

This is the first report, to our knowledge, on the incidence of hypoalbuminemia in patients with neuroblastoma. Hypoalbuminemia was a frequent finding at the diagnosis of neuroblastoma in our cohort, and PLE is likely one of the causes of hypoalbuminemia. We feel further study including larger number of patients is warranted to determine the incidence of hypoalbuminemia in neuroblastoma at diagnosis.

REFERENCES

1. Qian SY, Liu J. [Relationship between serum albumin level and prognosis in children with sepsis, severe sepsis or septic shock]. Zhonghua Er Ke Za Zhi. 2012; 50: 184-187.

2. Garg T, Chen LY, Kim PH, Zhao PT, Herr HW, Donat SM. Preoperative serum albumin is associated with mortality and complications after radical cystectomy. BJU Int. 2014; 113: 918-923.

3. Uppal S, Al-Niaimi A, Rice LW, Rose SL, Kushner DM, Spencer RJ, et al. Preoperative hypoalbuminemia is an independent predictor of poor perioperative outcomes in women undergoing open surgery for gynecologic malignancies. Gynecol Oncol. 2013; 131: 416-422.

4. Merritt RJ, Kalsch M, Roux LD, Ashley-Mills J, Siegel SS. Significance of hypoalbuminemia in pediatric oncology patients--malnutrition or infection? JPEN J Parenter Enteral Nutr. 1985; 9: 303-306.

5. Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. Hematol Oncol Clin North Am. 2010; 24: 65-86.

6. Citak C, Karadeniz C, Dalgic B, Oguz A, Poyraz A, Okur V, et al. Intestinal lymphangiectasia as a first manifestation of neuroblastoma. Pediatr Blood Cancer. 2006; 46: 105-107.

7. Braamskamp MJ, Dolman KM, Tabbers MM. Clinical practice. Protein-losing enteropathy in children. Eur J Pediatr. 2010; 169: 1179-1185.

8. Umar SB, DiBaise JK. Protein-losing enteropathy: case illustrations and clinical review. Am J Gastroenterol. 2010; 105: 43-49.

9. D'Amico MA, Weiner M, Ruzal-Shapiro C, DeFelice AR, Brodlie S, Kazlow PG. Protein-losing enteropathy: an unusual presentation of neuroblastoma. Clin Pediatr (Phila). 2003; 42: 371-373.

10. Coşkun T, Ozen H, Büyükpamukçu M, Kale G. Neuroblastoma presenting as protein-losing enteropathy. Turk J Pediatr. 1992; 34: 107-109.

11. Gerdes JS, Katz AJ. Neuroblastoma appearing as protein-losing enteropathy. Am J Dis Child. 1982; 136: 1024-1025.

12. Schussheim A. Protein-losing enteropathies in children. Am J Gastroenterol. 1972; 58: 124-132.

13. Grier JF. WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome: clinical features, diagnosis, and treatment. South Med J. 1995; 88: 22-24.

14. Krejs GJ. VIPoma syndrome. Am J Med. 1987; 82: 37-48.

15. Kim SY, Kwon JG, Kim MH, Oh JY, Park JH, Park KC, et al. [A case of acute lymphoblastic leukemia presenting with protein-losing enteropathy]. Korean J Gastroenterol. 2012; 60: 320-324.

16. Yamamoto M, Nishibuchi I, Matsuyama A, Okazaki J, Utsunomiya T, Tsutsui S, et al . Gastric carcinoma with protein-losing gastroenteropathy: report of a case. Surg Today. 2011; 41: 125-129.

17. Hwang YY, Leung AY, Ng IO, Chan GS, Chan KW, Tse E, et al. Protein-losing enteropathy due to T-cell large granular lymphocyte leukemia. J Clin Oncol. 2009; 27: 2097-2098.

18. Nomura Y, Abe M, Miyawaki K, Kenemitsu D, Tomikashi K . A patient with protein-losing colon cancer with massive ascites who was successfully treated by surgical resection of the tumor. Endoscopy. 2006; 38: 63-64.