Case report

Protein-losing enteropathy as a rare manifestation of neuroblastoma: a case report

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Abstract:

An 11-month-old girl presented with generalized edema, fever and secretory diarrhea. Investigations revealed fat malabsorption and hypoalbuminemia; protein-losing enteropathy was confirmed with a Tc-99m albumin scan, and subsequent endoscopy with biopsy was performed, which revealed intestinal lymphangiectasia without evidence of malignancy. She was initially treated for primary intestinal lymphangiectasia with intravenous albumin and fat-free enteral feeding without improvement. After two months of hospitalization, a scalp nodule was noticed, and the biopsy result was consistent with neuroblastoma. Staging was completed, revealing the primary tumor had originated from the left adrenal gland with multiple extensive local and distant metastases. She received induction chemotherapy and partial tumor removal followed by one cycle of consolidative chemotherapy. Unfortunately, she was lost to follow-up and died approximately one year after diagnosis.

Keywords : ● *Neuroblastoma* ● *Protein-losing enteropathy* ● *Intestinal lymphangiectasia* ● *Children*

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รายงานผู้ป่วย

Protein-losing enteropathy as a rare manifestation of neuroblastoma: a case report

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บทคัดย่อ

ผู้ป่วยเด็กหญิงอายุ 11 เดือน เข้ารับการรักษาตัวในโรงพยาบาลด้วยอาการบวมทั่วตัว ไข้ และถ่ายเหลวเป็นน้ำแบบ secretory ผลการตรวจทางห้องปฏิบัติการพบภาวะอัลบูมินในเลือดต่ำและมีการดูดซึมไขมันบกพร่อง เข้าได้กับภาวะโปรตีนรั่วเข้าโพรงลำไส้ ซึ่งได้รับการตรวจยืนยันด้วยอัลบูมินสแกน (Tc-99m albumin scan) รวมถึงการส่องกล้องทางเดินอาหารและตัดชิ้นเนื้อส่งตรวจทางพยาธิวิทยา พบว่าเข้าได้กับภาวะโป่งพองของหลอดน้ำเหลืองในทางเดินอาหาร (intestinal lymphangiectasia) และตรวจไม่พบมะเร็ง ผู้ป่วยได้รับการวินิจฉัยภาวะโป่งพองของหลอดน้ำเหลืองในทางเดินอาหารชนิด primary และได้รับการรักษาด้วยอัลบูมินทดแทนทางหลอดเลือดดำร่วมกับอาหารที่ไม่มีส่วนประกอบของไขมัน แต่ผู้ป่วยยังคงมีอาการบวมและถ่ายเหลวอย่างต่อเนื่อง หลังจากเข้ารับการรักษาตัวในโรงพยาบาลนาน 2 เดือน สังเกตว่ามีก้อนนูนเกิดขึ้นบริเวณหน้าผากผู้ป่วย ผลการตัดชิ้นเนื้อส่งตรวจทางพยาธิวิทยาเข้าได้กับมะเร็งชนิด neuroblastoma จึงได้ส่งตรวจทางรังสีวิทยาเพิ่มเติมพบก้อนมะเร็งที่ต่อมหมวกไตด้านซ้าย ร่วมกับการลุกลามเฉพาะที่และการแพร่กระจาย ผู้ป่วยได้รับยาเคมีบำบัดชนิด induction และเข้ารับการผ่าตัดก้อนมะเร็งออกบางส่วน ต่อด้วยยาเคมีบำบัดชนิด consolidation จำนวน 1 ชุด หลังจากนั้นผู้ป่วยไม่ได้มาติดตามตามนัดและเสียชีวิตหลังได้รับการวินิจฉัย 1 ปี

คำสำคัญ : ● *นิวโรบลาสโตมา* ● *ภาวะโปรตีนรั่วเข้าโพรงลำไส้* ● *ภาวะโป่งพองของหลอดน้ำเหลืองในทางเดินอาหาร* ● *ผู้ป่วยเด็ก*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2563;30:91-6.

Introduction

Neuroblastoma is the most common extracranial solid tumor among children; it originates from primordial neural crest cells. The initial presentations vary based on the location of the primary tumor and metastatic sites. Nonspecific systemic symptoms are commonly seen among patients with metastasis; approximately one half of patients have distant metastasis at diagnosis.[1-2] Neuroblastoma is also associated with paraneoplastic syndromes such as the opsoclonus-myoclonus-ataxia syndrome and intractable diarrhea secondary to the presence of the vasoactive intestinal peptide (VIP) from tumor cells, which has been occasionally reported among children with neuroblastoma.[3] However, protein-losing enteropathy (PLE) as the first manifestation has rarely been reported. In this report, we describe an unusual case of PLE due to secondary intestinal lymphangiectasia in a child with neuroblastoma.

Case report

An 11-month-old girl was admitted with generalized edema for one month and fever with watery diarrhea for two days. Physical examination revealed generalized edema, marked distension of the abdomen, and the presence of shifting dullness. The complete blood count (CBC) findings were: hemoglobin (Hb), 7.5 g/dL; white blood cell (WBC) count, 6.7 x10^9/L with neutrophils, 60%, bands, 9%, lymphocytes, 29%, myelocytes, 1% and metamyelocytes, 1%; 18 nucleated red blood cells (NRBC)/100 WBC; platelets, 129 x10^9/L and reticulocytes, 5.3%. She had a low albumin level (1.5 g/dL) and a slightly elevated level of aspartate aminotransferase (56 U/L) without hyperbilirubinemia. The stool exam revealed numerous fat globules without WBC or RBC. Renal function test and urinalysis were normal. Therefore, the etiology of generalized edema was suspected to be hypoalbuminemia secondary to gastrointestinal (GI) protein loss, confirmed with a Tc-99m albumin scan. An esophagogastroduodenoscopy with duodenal biopsy was performed, revealing dilated lacteals in the mucosa,

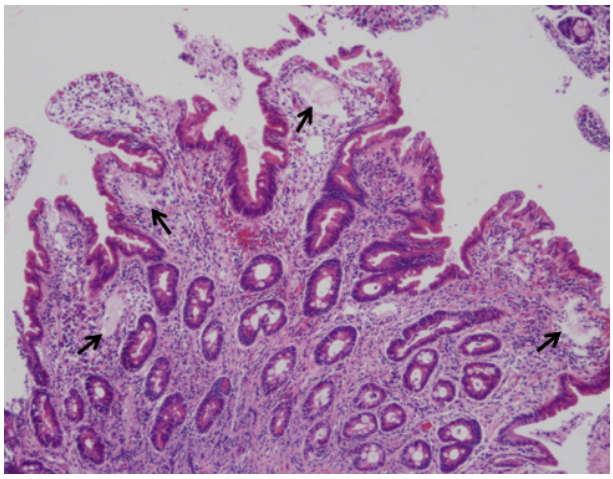

Figure 1 Small bowel mucosa revealing dilated lacteals (arrows) (HE x 100)

but without villous blunting, increased presence of intra-epithelial lymphocytes, granuloma, parasites or malignancy were identified; these findings were consistent with intestinal lymphangiectasia (Figure 1). The provisional diagnosis of primary intestinal lymphangiectasia was made, and she was initially treated with intravenous albumin and enteral feeding with Pan-Enteral, a formula containing medium-chain triglycerides, along with intravenous antibiotic therapy for presumed sepsis.

One month later, her clinical condition did not improve due to persistent hypoalbuminemia. Therefore, she was placed on parenteral nutrition (PN) and trophic tube feeding with a fat-free modular diet to prevent intestinal villous atrophy. She received intermittent albumin infusion every few days to maintain her albumin levels. After two months of hospitalization, a scalp nodule appeared on her forehead, and a repeated CBC revealed Hb, 10.9 g/dL; WBC 5.7 x10^9/L with neutrophils, 60%, bands, 15%, lymphocytes, 22%, myelocytes, 1% and metamyelocytes, 2%; 5 NRBC/100 WBC, and a platelet count of 50 x10^9/L. Hence, the pediatric hemato-oncologist was consulted to evaluate the abnormal CBC. The skull films revealed diffuse permeative osteolytic lesions involving parieto-temporal bones and the left mandibular ramus; the urine vanillylmandelic acid level was markedly elevated (326.9 μg/mg of creatinine), but the bone marrow aspiration was normal. A biopsy of the scalp nodule revealed poorly differentiated neuroblastoma,

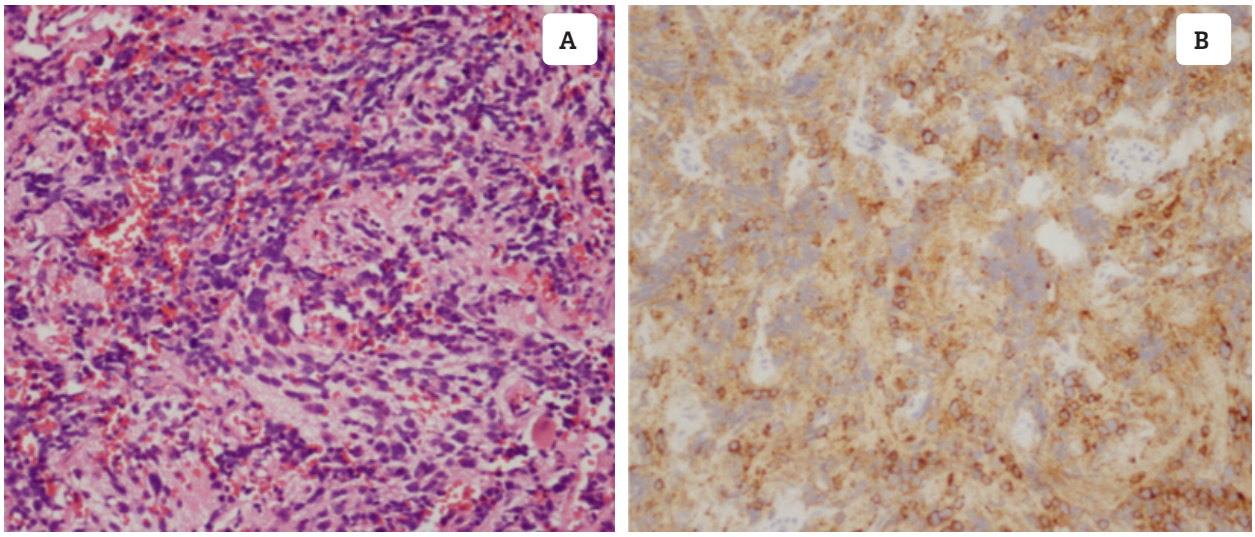

Figure 2 Poorly differentiated neuroblastoma with small-sized tumor cells (**A**) (HE x 200); immunohistochemical stain result positive with CD56 (**B**)

and the immunohistochemical stains were positive using chromogranin, synaptophysin, CD56, and neuron-specific enolase (NSE) (Figure 2).

Diagnostic imaging for neuroblastoma staging was completed. Computed tomography (CT) scan of the chest and abdomen revealed a heterogeneous enhancing mass 9.2x5.6x8.1 cm in size originating from the left adrenal gland with multiple vessel encasement and invasion, and paravertebral masses along the T6-L2 levels with epidural extension. Also, evidence was found of liver and intra-abdominal and left supraclavicular nodes as well as multiple bone metastases on the 99mTc-MDP bone scintigraphy and I-131 metaiodobenzylguanidine (MIBG) scan. Moreover, a CT scan of the brain was performed due to the finding of bilateral gaze palsy. It revealed multiple epidural calcified masses (2.5 to 3.5 cm) along the bilateral cerebral convexities, the vertex and both the temporal and occipital regions, extending through the skull sutures and protruding as soft-tissue masses (8 to 13 mm) on the left side of the forehead and the left temporal region, as well as the lateral aspects of both orbits with associated permeative calvarial destruction, suggestive of brain metastasis.

High risk neuroblastoma stage 4 was diagnosed according to the International Neuroblastoma Staging System and she received induction chemotherapy consisting of cisplatin, etoposide, doxorubicin and cyclophosphamide. After the first cycle of chemotherapy, her albumin level improved to the point of resolving her edematous status and diarrhea without albumin-replacement therapy. The modular diet was gradually titrated from trophic feeding until full enteral feeding; PN was discontinued three weeks after the commencement of chemotherapy, and fat-containing diets were well-tolerated without steatorrhea subsequently. She underwent a partial tumor removal after 4 cycles of induction chemotherapy followed by 2 additional cycles of induction chemotherapy. The refractory chemotherapy regimen containing ifosfamide, carboplatin and etoposide was initiated as consolidative therapy for the large unresectable tumor. Unfortunately, she was lost to follow-up after the first cycle of the refractory chemotherapy regimen and died at home approximately one year after diagnosis.

Discussion

PLE is a condition characterized by protein loss in the GI tract leading to decreased serum protein levels, and can be complicated by edema, ascites, pleural and pericardial effusions and malnutrition. The causes of PLE can be divided in two groups based on disease mechanisms: mucosal injury and lymphatic abnormalities. Abnormalities of the lymphatic vessels in the GI tract,

also known as intestinal lymphangiectasia, are a condition characterized by a local or diffuse dilatation of lacteals leading to their rupture and the leakage of protein and fat-rich lymph fluid in the GI tract. Intestinal lymphangiectasia can be classified in primary (congenital malformation of lymphatic vessels or Waldmann's disease) and secondary intestinal lymphangiectasia, caused by either lymphatic obstruction or elevated lymphatic pressure.[4,5]

Tumors, like neuroblastoma, metastatic melanoma, lymphoma, leukemic involvement, Langerhans cell histiocytosis, lymphangioma, hemangioma and Kaposi sarcoma, are one of the causes contributing to intestinal lymphatic compression and obstruction.[6] Eight cases of PLE secondary to neuroblastoma have been reported in the medical literature between 1980 and 2020 (Table 1). The proposed pathophysiologies of PLE among these patients are either intestinal lymphangiectasia secondary to lymphatic obstruction (7 cases including our case) or neurohumoral effect due to tumor-related VIP or catecholamine excess (1 case).[7-14] The diagnosis of neuroblastoma among patients with PLE requires a high index of suspicion owing to the fact that its presentation might be primarily a gastrointestinal manifestation. Therefore, excluding secondary causes with appropriate

Table 1 Reported cases of neuroblastoma presenting with protein-losing enteropathy

No.	Study	Age (months)	Sex	Gut biopsy	Cause of PLE	Stage (risk)	Treatment	Status
1.	Schussheim (1972)[7]	36	F	Done	Intestinal lymphangiectasia	N/A	N/A	N/A
2.	Gerdes et al. (1982)[8]	8	F	-	Intestinal lymphangiectasia	4	Multi-agent CMT	Remission, off CMT at 26 months old
3.	Coskun et al. (1992)[9]	30	F	-	Neurohumoral effect	N/A	N/A	N/A
4.	Reifen et al. (1994)[10]	8	F	Done	Intestinal lymphangiectasia	N/A	N/A	N/A
5.	D'Amico et al. (2003)[11]	14	M	-	Intestinal lymphangiectasia	3 (IR)	8 cycles of carbo + eto / carbo + doxo + CTX followed by tumor removal	Remission, off CMT
6.	Citak et al. (2006)[12]	12	F	Done	Intestinal lymphangiectasia	4	N/A	N/A
7.	Brenner et al. (2016)[13]	6	F	Done	Intestinal lymphangiectasia	4 (IR)	6 cycles of carbo + eto + doxo + CTX followed by tumor removal	Alive, on CMT at 9 months old
8.	Navalkele et al. (2016)[14]	11	F	-	Intestinal lymphangiectasia	4 (IR)	8 cycles of carbo + eto + doxo + CTX, tumor removal and 6 cycles of maintenance therapy with isotretinoin	Alive, 11 months off CMT
9.	Our case (2020)	11	F	Done	Intestinal lymphangiectasia	4 (HR)	4 cycles of CDDP + eto + doxo + CTX, partial tumor removal then 2 additional cycles and ICE x 1	Lost to follow-up, died at 24 months old

Carbo, carboplatin; CDDP, cisplatin; CMT, chemotherapy; CTX, cyclophosphamide; doxo, doxorubicin; eto, etoposide; HR, high risk; ICE, ifosfamide + carboplatin + etoposide; IR, intermediate risk; N/A, not available; PLE, protein-losing enteropathy.

investigations is important, such as echocardiography to assess the cardiac function and radiographic studies like CT scan or magnetic resonance imaging to localize the intestinal area of involvement or evidence of external compression of lymphatic vessels, before making the diagnosis of primary intestinal lymphangiectasia.[6]

In our case, immature forms of RBC and WBC were detected in the CBC, the so-called 'leukoerythroblastic blood picture', at presentation, which remains an important clue for general pediatricians to raise the suspicion of metastatic tumors involving the bone marrow. In four previously-reported cases[8,10,12,13], a diagnosis of primary intestinal lymphangiectasia was made initially, but signs and symptoms like a palpable abdominal mass, hypertension, calcification on a plain abdominal radiograph and periorbital ecchymosis with obstructive jaundice suggested neuroblastoma developed later. Therefore, a repeated physical examination along with further investigations such as abdominal imaging to evaluate potential secondary causes are important among patients with diagnosis of primary intestinal lymphangiectasia, particularly in refractory cases.

Conclusion

PLE is a rare manifestation among children with neuroblastoma. For children, who are refractory to the standard treatments for primary intestinal lymphangiectasia, neuroblastoma should be included in the differential diagnosis list.

Conflict of interest

This case report has no financial commercial interests.

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