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Olgu Sunumu / Case Report

Management of VIP Associated Diarrhea in a Case with Neuroblastoma

Nöroblastomlu Bir Olguda VİP İlişkili Diyarenin Yönetimi

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ABSTRACT

Watery diarrhea associated with hypokalemia and achlorhydria (WDHA) syndrome is commonly caused by vasoactive intestinal peptide (VIP) secreting tumors in adults and generally associated with neural crest tumors in pediatric population. VIP secretion is associated with neuroblastic cell differentiation. Octreotide treatment can be a choice for diarrhea in such cases. However, its benefit is controversial and surgery is usually needed. A 14-month-old female with diagnosis of inoperable undifferantiated intraabdominal neuroblastoma who developed chronic diarrhea at first year of chemotherapy is reported. Octreotide treatment was used to control diarrhea. Because of the failure of octreotide treatment, debulking surgery was performed and diarrhea subsided after the surgery.

Key Words: Neuroblastoma, diarrhea, octreotide

ÖZET

Diyare ilişkili hipokalemi ve aklorhidri sendromu (WDHA) erişkinlerde çoğunlukla vazoaktif intestinal peptit (VIP) salgılayan tümörlere, çocuklarda ise nöral krest tümörlerine bağlı olarak ortaya çıkmaktadır. VIP salgılanması nöroblastik hücre diferansiyasyonu ile ilişkilidir. Somatostatin analoğu olan ve VIP etkisini antagonize eden oktreotit, bu tür vakalarda diyareye yönelik bir tedavi seçeneği olabilir. Ancak tedavideki yararı tartışmalı olup, hastaların çoğunda diyare cerrahiden sonra geçmektedir. Burada kemoterapisinin 1. yılında kronik diyare gelişen, total kitle rezeksiyonu için uygun olmayan, intraabdominal nöroblastomlu 14 aylık bir kız hastadaki diyare yönetimi sunulmuştur.

Anahtar Kelimeler: Nöroblastom, diyare, oktreotit

INTRODUCTION

Neuroblastic tumors cause different kinds of paraneoplastic syndromes. One of them is watery diarrhea associated with hypokalemia and achlorhydria (WDHA) syndrome that is a rare condition secondary to vasoactive intestinal peptide (VIP) secretion. WDHA syndrome was first described by Verner and Morrison in 1958[1] in association with non-insulin secreting islet cell adenomas of pancreas. Pediatric cases are generally related with neural crest tumors in contrast to adults. Pancreatic VIPoma cases respond well to octreotide treatment but it was shown to be ineffective in previously reported neuroblastic tumors[2]. We report a 14-month-old female with watery diarrhea due to VIP secreting neuroblastoma and use of octreotide for controlling diarrhea.

Case Report

A 14-month-old female treated for urinary tract infection in another hospital, was transfered to our hospital after detection of a mass near the inferior pole of left kidney, bilateral nephromegaly

and left hydroureteronephrosis on abdominal ultrasound. Abdominal computed tomography revealed a calcificated mass extending to right paraaortic, paracaval, parailiac areas. MIBG (Methyliodobenzylguanidin) scintigraphy revealed MIBG enhancement of mass. A true-cut biopsy was performed and histopathologic examination was consistent with undifferentiated neuroblastoma. Skeletal survey, thoracal computed tomography imaging findings were unremarkable and bone marrow aspiration was normal. With a stage 3 neuroblastoma and older than 1 year, she was assumed as high risk group according to "Turkish Pediatric Oncology Group" Neuroblastoma study[3]. Because of abnormal kidney function tests, chemoterapy doses were decreased by 25% and given per kilogram. After the two courses of vincristine, ifosfamide, dacarbazine, adriamycin, and two courses of cysplatine, cyclophosphamide and etoposide, a decrease in size of mass was noticed. Due to localization of tumor, complete surgical resection was not possible. After 4 courses of chemotherapy, tubular nephrotoxicity developed and treatment was modified. After the six courses of chemotherapy, abdominal tomography showed stable sized tumor. 100 mCi I-131 MIBG treatment was applied then continued with six months of retinoic acid (100mg/m^2) treatment. Treatment was cessated 18 months after the onset of first symptoms, with a stable calcificated mass, normal urinary VMA and ferritin. Diarrhea which occured occasionally begining with second course of chemotherapy, became permanent at the completion of first year with a frequency of 5-6 times per day. The stool culture, parasitic tests, gastroduodenoscopy and colonoscopy were normal. Three months after the chemotherapy cessation, her diarrhea had been continuing. Serum VIP level was 137 pg/ml (normal range 33-63). Therefore, octreotide infusion (1 mcgr/kg/hr) following a subcutaneous maintenance dose of 1 mg two times per day was started. Three months later octreotid was stopped because of continuing diarrhea. Surgery was performed 29 months after diagnosis and 90 % of tumor tissue was resected, histopathologically surgical borders were positive for tumor. Soon after surgery the diarrhea subsided. Pathological examination revealed neuroblastoma tissue with ganglionic differentiation. Radiotherapy with a dose of 2100 cGy to T12-S2 region was administered.

DISCUSSION

VIP secreting tumors are rarely seen at chilhood period. VIP is a 28-amino acid peptide stimulates intestinal water and electrolyte secretion by activating adenylate cyclase and cyclic adenosine monophosphate in intestinal cells[4]. This stimulation results in secretory diarrhea, dehydratation and hypokalemia. Most common VIP secreting tumors during chilhood are ganglioneuroma and ganglioneuroblastoma[5]. Patients may present with diarrhea either before chemotherapy or during treatment. Bourdeaut et al.[2] reported 6 cases of neuroblastoma experienced diarrhea after starting chemotherapy, 5 of whom were histologically poorly differentiated at initial examination and histologic examination after chemotherapy showed a more differentiated phenotype with high serum VIP levels. As mentioned, our patient's biopsy specimen was consistent with undifferentiated neuroblastoma at diagnosis and chronic diarrhea began during chemoterapy. In time, amount of calcification increased radiologically and partial ganglionic differantiation was detected at last histopathological examination. Previous studies have shown the correlation of increased VIP levels with cell differantiation in newly diagnosed neuroblastoma cases[6]. Also Pence et al[7] have revealed that VIP has a role in initiating or promoting differentiation of neuroblastoma cells, and supression of proliferation.

Octreotide is a somatostatin analogue shown to be therapeutically benefical in reducing symptoms related to gastroenteropathic endocrine tumors such as VIPomas. The various actions of

somatostatin are mediated through specific membrane receptors. Five subtypes of somatostatin receptors have been identified[8]. Oda et al[9] reported that efficacy of somatostatin analogues might depend on presence of somatostatin receptors and degree of expression on tumor cell surface, especially in subtypes of 2 and 3. Previous reports have also indicated failure of octreotide treatment in neural crest tumors similarly to our case[2]. VIP secreting neural crest tumors can express less and different somatostatin receptors than other VIPomas, which may be the cause of treatment failure. Surgery shoud be purposed as first line treatment in VIP secreting neural crest tumors, but in case of unresectable or metastatic tumors, debulking resection may be considered to relieve such paraneoplastic symptoms.

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