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Bevacizumab-Associated Bowel Microperforation in a Patient with Neuroblastoma

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Abstract

The anti-vascular endothelial growth factor antibody bevacizumab is effective against several malignancies in adults but unproven in pediatric oncology. In early phase pediatric studies toxicities were similar to those in adults. Bowel perforation in adults is a rare but serious toxicity, but has not been hitherto reported in children. A five-year-old male with chemoresistant neuroblastoma treated with bevacizumab plus radioimmunotherapy developed acute abdominal pain. CT scan showed free abdominal air and pneumatosis coli. Emergency laparotomy and bowel diversion was performed leading to complete recovery and timely continuation of anti-neuroblastoma therapy. Early recognition and rapid intervention can prevent a catastrophic outcome in bevacizumab-related bowel perforation.

Keywords

neuroblastoma; bowel perforation; bevacizumab; pediatrics

Introduction

Vascular endothelial growth factor (VEGF), a tumor angiogenesis regulator stimulates proliferation of cancer cells and new blood vessel formation. VEGF and VEGF-receptor expression correlates with higher stage and poorer prognosis in neuroblastoma.¹ Bevacizumab, a humanized anti-VEGF monoclonal antibody inhibits tumor vasculature and proliferation, and is currently approved by the US Food and Drug Administration for the treatment of several malignancies in adults.² In children the recommended phase II dose is 15mg/kg. Common adverse events reported in the initial phase I³ and subsequent phase II studies were similar in incidence and severity to those encountered in adults and included epistaxis, hypertension and proteinuria.^{4,5} In adults, a rare but serious complication in bevacizumab-treated patients is bowel perforation which occurs even in patients without gastrointestinal malignancies. The incidence in large series was reported to be 1–6%^{6,7} with

a perforation-associated mortality rate of 21.7%.⁸ The etiology of bevacizumab-related bowel perforation is unclear: hypotheses include ischemia of gut microvasculature, thromboses in mesenteric or splanchnic blood vessels⁹, impaired healing of gastrointestinal mucosa¹⁰, or regression of normal bowel blood vessels leading to poor bowel wall perfusion and perforation.¹¹ The latter mechanism could be especially significant in children in whom interference with growing blood vessels could significantly impact organ development. We report a case of bowel microperforation and its management in a child treated with bevacizumab.

Case Report

A 3.5 year old male patient presented at an outside institution with a large abdominal mass and bone and bone marrow metastases. Diagnosed with high-risk *MYCN*-non-amplified stage 4 neuroblastoma, he was treated in accordance with Children's Oncology Group protocol A3973¹². He had an incomplete response to therapy with persistent osteomedullary disease and moderate reduction in size of primary tumor after cycle 5. He then underwent partial resection of the primary tumor, Roux-en-Y reroute of pancreatic duct and partial pancreatic resection. Post-operative course was marked by intermittent, though persistent, diarrhea, hyperbilirubinemia and bile duct stricture requiring repair. He was then referred to our institution where he received further chemotherapy with cyclophosphamide plus topotecan¹³, and, high-dose cyclophosphamide plus irinotecan and vincristine ($\times 2$ cycles),¹⁴ and underwent gross total surgical resection of residual neuroblastoma. However he had persistent, multifocal, chemorefractory osteomedullary disease on ¹²³I-metaiodobenzylguanidine (MIBG). He then was enrolled on a phase I study of ¹³¹I-3F8-mediated radioimmunotherapy and bevacizumab (NCT00450827). The rationale for combination of radioimmunotherapy and anti-angiogenesis was based on preclinical data suggesting synergy of the two modalities. He received 128 mCi (6mCi/kg) ¹³¹I-3F8 on day 0 and bevacizumab 15 mg/kg on days 1 and 15. He tolerated therapy without unexpected adverse events; however 12 days after the second dose of bevacizumab developed acute, diffuse abdominal pain. On examination, the abdomen was tender and firm with decreased bowel sounds. CT scan, performed within 6 hours after onset of symptoms, revealed several new findings that had not been noted on CT abdomen and pelvis done 12 days prior to initiating bevacizumab: a complex extraluminal collection in the anterior upper abdomen containing air and debris consistent with a loculated collection following a bowel perforation had developed. In addition, edema of the transverse colonic wall, extensive pneumatosis coli and ascites were noted (Figure 1). Bowel perforation was diagnosed and he underwent emergent laparotomy via a small right lower quadrant incision. Extensive small bowel adhesions and colonic pneumatosis were observed though a specific perforation was not visualized. A major laparotomy was not attempted due to the risks related to radioimmunotherapy-related myelosuppression, platelet count at time of surgery being 33,000/ml. A double-barrel loop ileostomy and aspiration of left upper quadrant collection were performed without complications. Post-operative care included metronidazole, gentamicin, and piperacillin/tazobactam. Post-operative course was uncomplicated despite expected neutropenia (nadir absolute neutrophil count 500/ μ L 4 days post-surgery). CT scan performed on post-operative day 35 showed resolution of pneumatosis coli and free air. New

pan-colonic wall thickening and narrowing were observed. Colonoscopy confirmed colonic stricture proximal to the hepatic flexure. Protocol therapy was subsequently discontinued. He continued to make a rapid clinical recovery and received cyclophosphamide (70mg/kg/day $\times$ 2) 15 days after surgery followed by autologous stem cell rescue to reverse myelosuppression. Over the next four years he continued to receive effective anti-neuroblastoma treatment including abdominal radiotherapy, anti-GD2 antibody 3F8 plus sargramostim¹⁵ and the AKT-inhibitor perifosine¹⁶ at the end of which he was deemed to have no active disease: no evidence of neuroblastoma in bone marrow, persistent low intensity skeletal uptake on MIBG but no uptake on FDG-PET scan. Serial colonoscopies showed resolution of colonic thickening and stricture. Sixteen months after bowel perforation he underwent colonoscopic reanastomosis with reversal of ileostomy. He continued to need prolonged nutritional support initially with parenteral nutrition for 6 years post-surgery and then with elemental G-tube feeds. Currently at age 14 years, he tolerates oral nutrition, has been off neuroblastoma therapy for 3.5 years, attends school regularly and is on 25th and 10th percentiles for height and weight respectively.

Discussion

Inhibiting tumor angiogenesis has the potential to improve outcomes in high-risk pediatric malignancies such as neuroblastoma. Our experience⁵ and that of other pediatric oncologists thus far¹⁷, indicates that adverse events related to bevacizumab are similar to those observed in adults. Adults with bevacizumab-related bowel perforation usually present with acute abdominal pain, fever, nausea, or vomiting in the days or weeks post treatment¹⁸, as was observed in our patient. Previous abdominal radiotherapy and bowel surgery are known risk factors.⁸ Our patient previously had upper gastrointestinal tract surgery on the small intestine in an attempt to resect peri-pancreatic neuroblastoma. We did not encounter bowel perforation in 33 neuroblastoma patients treated with the combination of irinotecan, temozolomide and bevacizumab⁵ nor in 23 other neuroblastoma patients treated with radioimmunotherapy plus bevacizumab on the same study as the described patient (unpublished data). However, none of the above patients had undergone bowel surgery.

Due to a high index of suspicion, we were able to diagnose bowel perforation by CT imaging very soon after the onset of symptoms, and rapid surgical intervention was initiated despite significant thrombocytopenia. Adults with bevacizumab-related bowel perforation have been managed successfully with either operative interventions (bowel resection or intestinal diversion)¹⁹ or conservatively (nasogastric tube and percutaneous abdominal catheter insertions). The decision to operate in our patient was based on the impressive radiological findings and symptoms, and the urgency to continue with anti-neuroblastoma therapy for chemorefractory high-risk disease. Surgery resulted in salvage with minimal post-operative complications. However, management decisions in children with bevacizumab-related bowel perforation should be made on a case-by-case basis considering factors including severity of the perforation and the clinical condition of the patient.

There is a higher incidence of poor wound healing, gastrointestinal fistulae and other post-operative complications if surgery is performed soon after bevacizumab therapy. However, in our patient, despite the fact that perforation occurred within about one half-life of

bevacizumab circulation in children (estimated at 11.8 days³), there was rapid wound healing and post-operative recovery facilitating timely continuation of anti-neuroblastoma therapy. It is possible that early diagnosis and intervention contributed to the successful outcome to a potentially devastating event.

Ours is the first reported case of a child with bevacizumab-associated bowel perforation. With increasing use of bevacizumab and other anti-angiogenic agents²⁰ in children, further cases of bowel perforation will come to light. Early recognition of this rare though potentially catastrophic complication may prevent severe morbidity and mortality in children receiving anti-angiogenic therapy. Before initiating unproven therapies in children with cancer, it is important to weigh their risks and benefits and consider their use under the auspices of a clinical trial which will facilitate close monitoring of the patient.

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Figure 1. Contrast-enhanced CT of the abdomen. Axial view showing pneumatosis coli of the right colon (arrows) (A), sagittal view showing collection (arrows) superior to the transverse colon (arrowheads) (B) and axial view showing collection (arrows) and ascites (C).