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CASE REPORT

Lethal biliary sepsis in a patient with pancreatic neuroendocrine tumor treated with everolimus

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Abstract

We report a case of a patient with recurrent biliary tract infection (BTI) after endoscopic biliary stenting due to obstructive jaundice caused by pancreatic neuroendocrine neoplasm. The patient developed lethal biliary sepsis after the initiation of everolimus, despite the normal function of a endobiliary stent. Our case suggests that immunosuppression caused by everolimus may be associated with severe BTI in patients with endobiliary stents. Patients with endobiliary stents treated with everolimus should be carefully monitored in order to detect signs of BTI as soon as possible. Retrospective data exploration and prospective trials should be performed in order to elucidate the link between everolimus and BTI in patients with endobiliary stents.

Key words: Everolimus; biliary tract; infection; cholangitis; endobiliary stenting; neuroendocrine neoplasm

1. Introduction

Nonfunctional pancreatic neuroendocrine neoplasms (panNENs) present with jaundice in 25–40% of patients [1]. Systemic first-line treatment in patients with metastatic panNENs consists of somatostatin analogs, everolimus, and sunitinib in G1 and G2 panNENs and cisplatin-/etoposide-based chemotherapy in G3 panNENs [2]. However, treatment of obstructive jaundice should be performed before systemic treatment.

Endoscopic biliary stenting is the most common treatment for patients suffering from obstructive jaundice associated with malignant hepatobiliary tumors [3]. However, the rate of complications is still very high. Stent dysfunction occurs in almost half of patients [3] and biliary tract infection (BTI) in one-quarter of patients treated with plastic stents within the next 120 days after the stent placement [4]. BTI after billiary stenting with plastic stents strongly correlates with stent dysfunction. It is most likely associated with microbial biofilm which progressively increases in thickness [5].

Everolimus inhibits Mammalian target of rapamycin and has a significant antiproliferative effect on pancreatic neuroendocrine tumor cell lines [6]. However, treatment side-effects are common and lead to temporary treatment discontinuation in up to 60% of patients [7], while infections requiring antibiotic treatment occur in 23% of patients. Although one-quarter of patients with panNENs present with obstructive jaundice, which often requires endoscopic biliary stenting, neither one study has previously reported the incidence of BTI in patients receiving everolimus.

2. Case Report

We report a case of a 54-year old male patient was admitted due to obstructive jaundice. Medical history was unremarkable and the patient was not taking any medication. Laboratory examinations showed profoundly increased total serum bilirubin (374 μmol/L), alkaline phosphatase (ALP) of 652 U/L, alanine transaminase (ALT) of 52 U/L, and aspartate transaminase (AST) of 58 U/L and lactate dehidrogenase of 204 U/L. Abdominal ultrasound and computed tomography revealed a 45-mm × 30-mm large primary tumor in the pancreatic head, abdominal lymphadenopathy and multiple focal lesions in both liver lobes. Endoscopic retrograde cholangio-pancreatography showed significant stenosis of both left and right hepatic duct. Plastic endobiliary stent was placed in the right hepatic duct, but the placement in the left duct was not feasible. Bilirubin levels decreased to 152.8 μmol/L nine days after the procedure with marked improvement of clinical signs of cholestasis. Biopsy of the liver metastasis confirmed G2 neuroendocrine tumor, whereas Ki67 immunostaining was positive in 10% of tumor cells. Serum gastrin was normal and chromogranin A was >700 μg/L. Somatostatin-receptor scintigraphy showed grade 4 uptake both in the primary tumor and metastases. Hence, treatment with long acting ocreotide was initiated. Two months after the initiation of octreotide, he was readmitted due to acute cholangitis precipitated with biliary stent dysfunction. Dysfunctional stent from the right hepatic duct was replaced and the second plastic stent was successfully placed in the left hepatic duct. Treatment with amoxicillin + clavulonic acid and metronidazole led to normalization of inflammatory parameters. Bilirubin decreased to 66 μmol/L seven days after the procedure. Three months after the diagnosis, the patient was diagnosed with progressive disease. Everolimus was added to long-acting octreotide and the initial dose of 10 mg was well tolerated. Two months after the initiation of everolimus, he was readmitted due to fever with shaking chills, vomiting and intensive pain in his right upper abdomen. At readmission, his axillary temperature was 39.6°C, blood pressure 100/60 mmHg, heart rate 110 beats/min, and respiratory rate 28/min. Laboratory evaluation showed bilirubin 16 μmol/L, AST 72 U/L, ALT 64 U/L, gamma glutamyl transferase 380 U/L, ALP 750 U/L, leukocyte count 9.2 mmol/L, hemoglobin 86 g/L, and CRP 289.4 mg/L. Chest and abdominal rentgenogram along with urine analysis were normal, and there were no signs of bile duct dilatation on ultrasonography. Bacteriological analysis of his blood, urine, and stool samples was negative. He was diagnosed with biliary sepsis and treated with amoxicillin + clavulonic acid and metronidazole, while treatment with everolimus was stopped. The patient died 5 days after the admission and 6 months after the initial diagnosis.

3. Discussion

The most common adverse events of everolimus include stomatitis, anemia, thrombocytopenia, renal failure, and

pneumonitis [7]. To the best of our knowledge, this is the first report of BTI associated with the use of everolimus. Several issues need to be addressed in our case report. First, the diagnosis of biliary sepsis was made primarily based on symptoms and exclusion of infection in the most common sites. Despite the presence of clinical signs of systemic inflammatory response in our patients, blood cultures were negative, as seen in three-quarters of all patients with BTI. Another issue which needs to be addressed is normal bilirubin level and the absence of bile duct dilatation during sepsis. Normal bilirubin level implies normal function of biliary stents and one can expect increased serum bilirubin only if the stent dysfunction is the precipitating factor of BTI. The fact that the bilirubin level was normal have ruled out stent dysfunction as the precipitating factor for BTI and suggested that immunosuppression induced by everolimus could facilitate bacterial ascend from the gut, which may be the main precipitating factor of BTI. One could also raise concerns why we have not placed metal stents in the first place, since the expected life duration in our patient was longer than 4 months [3]? Placement of metal stents in patients with profound biliary stenosis is more challenging when compared with placement of plastic stents. The main goal was to place plastic stents in both left and right hepatic duct to dilatate stenosis, and hence that a metal stent could be placed in the second step. Unfortunately, the patient died 1 month before plan metal stent placement.

In conclusion, our case suggests that everolimus may be associated with severe BTI in patients with normal functioning endobiliary stents. Retsrospective data exploration and prospective trials should be performed to elucidate the link between everolimus and BTI in patients with endobiliary stents. Patients with endobiliary stents treated with everolimus should be carefully monitored to detect signs of BTI as soon as possible.

References

1. Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: Clinical features, diagnosis and medical treatment: Advances. Best Pract Res Clin Gastroenterol 2012;26:737-53. https://doi.org/10.1016/j.bpg.2012.12.003.
2. Pavel M, Valle JW, Eriksson B, Rinke A, Caplin M, Chen J, et al. ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms: Systemic therapy - biotherapy and novel targeted agents. Neuroendocrinology 2017;105:266-80. https://doi.org/10.1159/000471880.
3. Dumonceau JM, Tringali A, Blero D, Devière J, Laugiers R, Heresbach D, et al. Biliary stenting: Indications, choice of stents and results: European society of gastrointestinal endoscopy (ESGE) clinical guideline. Endoscopy 2012;44:277-98. https://doi.org/10.1055/s-0031-1291633.
4. van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010;362:129-37. https://doi.org/10.1056/NEJMoa0903230.
5. Donelli G, Guaglianone E, Di Rosa R, Fiocca F, Basoli A. Plastic biliary stent occlusion: Factors involved and possible preventive approaches. Clin Med Res 2007;5:53-60. https://doi.org/10.3121/cmr.2007.683.
6. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van CE, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514-23. https://doi.org/10.1056/NEJMoa1009290g.
7. Panzuto F, Rinzivillo M, Fazio N, Braud F, Luppi G, Zatelli MC, et al. Real-world study of everolimus in advanced progressive neuroendocrine tumors. Oncol Alpha Med Press 2014;19:966-74 https://doi.org/10.1634/theoncologist.2014-0037.