Ibrutinib-Induced Pancreatitis in Patients with Waldenstrom Macroglobulinemia

Waldenstrom Makroglobulinemisi Olan Hastalarda İbrutinib Kaynaklı Pankreatit

Nurhilal Büyükkurt[1], Barış Soydaş[2]

[1]Başkent University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Ankara, Türkiye
[2]Başkent University Faculty of Medicine, Department of Gastroenterology, Ankara, Türkiye

To the Editor,

Waldenstrom macroglobulinemia (WM) is a rare disorder [1]. The combination of rituximab and ibrutinib has been associated with prolonged progression-free survival in previously treated and untreated cases of WM [2]. Unfortunately, however, adverse effects due to off-target interactions are disadvantages of ibrutinib. In this context, we would like to present a case of pancreatitis in a patient undergoing ibrutinib treatment. The mechanism of pancreatitis may be direct toxicity, hypertriglyceridemia, or immune-mediated injury to the liver, pancreas, or blood supply by direct injection [3]. Although a single case of pancreatitis was reported in a phase 1/1b study that included 48 patients, ibrutinib-associated pancreatitis has not yet been reported in the literature as a real-life clinical experience [4].

A 76-year-old male patient with benign prostatic hyperplasia was evaluated for WM. Methylprednisolone was started at 1 mg/kg due to concomitant autoimmune hemolytic anemia. Unfortunately, there was no improvement of the anemia within 10 days and the patient was diagnosed with WM on December 10, 2020. He was then treated with a rituximab biosimilar (375 mg/m^2) plus bendamustine (90 mg/m^2). At 3-4 days after the first treatment, he developed joint pain and rashes on his legs. It was assumed that these were effects of serum sickness, a rare adverse event associated with rituximab infusion. Therefore, we treated him with a protocol of gradually decreasing doses of methylprednisolone every 7 days. We used another biosimilar form of rituximab in the second and third cycles but the patient did not want to continue this protocol due to the side effects. Therefore, ibrutinib treatment was begun and he had a partial response after three courses of treatment. However, in the 18th month of treatment, he presented with epigastric pain, nausea, and abdominal pain for 1 week. As a result of physical examination and initial laboratory tests, we detected significantly elevated amylase and lipase levels (297 U/L and 597 U/L, respectively). In an evaluation for possible pancreatitis, there was no history of hyperlipidemia, no abdominal trauma, and no family history; his triglyceride levels were normal, he had stopped consuming alcohol approximately 2 years ago, and he had undergone a cholecystectomy 6 years ago. By abdominal ultrasound the common bile duct diameter was found to be 8.5 mm, no stones were observed, the intrahepatic bile ducts were normal, and pancreatic echogenicity was slightly heterogeneous. We consulted with a gastroenterology specialist and concluded that the symptoms were probably associated with the patient's targeted treatment agent. However, we did not find signs of the adverse reaction reported as pancreatitis related to ibrutinib in the literature, except for a single patient reported in a phase 1 study. Trimethoprim-sulfamethoxazole (TMP/SMZ) and valacyclovir, which had been used for a long period of time to prevent opportunistic infection, were discontinued due to possibly causing the adverse effect, and a decision was made for close follow-up. However, his amylase and lipase levels continued to increase after 3 days (315 U/L and 942 U/L, respectively). This process continued for about 10 days with clinical and laboratory findings; moreover, there were no detailed recommendations for the treatment of ibrutinib-induced pancreatitis in the aforementioned study. Therefore, his ibrutinib treatment was stopped and he was evaluated with magnetic resonance cholangiopancreatography (MRCP). There were no additional findings by MRCP to explain the pancreatitis. The patient's pancreatic enzymes dropped slowly after the cessation of ibrutinib (Figure 1) and clinical improvement was achieved. Pancreatitis was not encountered upon resumed administration of TMP/SMX and valacyclovir in the retreatment process.

Undesirable outcomes due to off-target effects such as bleeding, skin rash, and atrial fibrillation are among the disadvantages of ibrutinib. There are recommendations for the management of these side effects according to their severity. However, there is no information in the literature on the management of ibrutinib treatment for patients who develop acute pancreatitis. As abdominal pain, nausea, and vomiting can also be associated with cancer chemotherapy, the diagnosis of acute pancreatitis might be missed [3]. Drug-related causes of acute pancreatitis are rare (0.1%-2% of cases) but may occasionally be life-threatening [5]. The recognition of drugs with the potential to cause acute pancreatitis may help clinicians gain awareness and could prevent the unnecessary re-administration of medication [6].

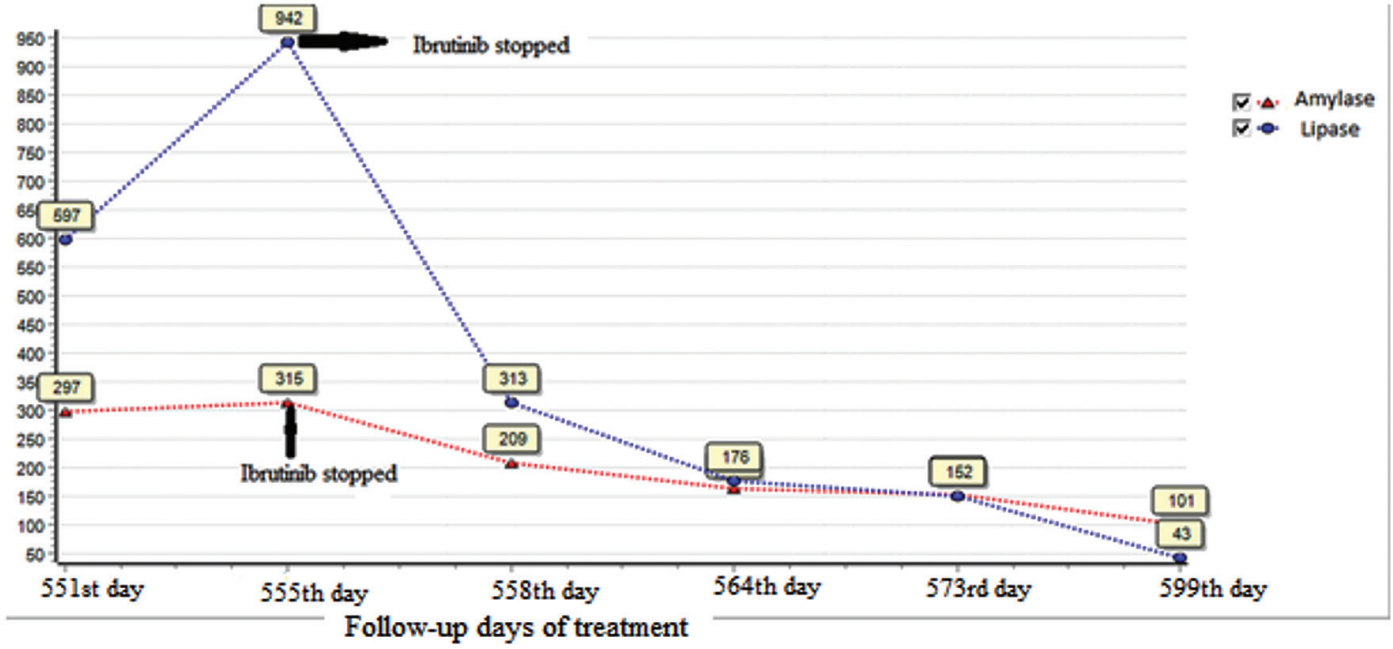

Figure 1. The course of serum amylase and lipase levels during acute pancreatitis and their relationship with ibrutinib.

Keywords: Waldenstrom macroglobulinemia, Ibrutinib, Pancreatitis

Anahtar Sözcükler: Waldenstrom makroglobulinemisi, İbrutinib, Pankreatit

Ethics

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: N.B., B.S.; Concept: N.B.; Design: N.B.; Data Collection or Processing: N.B., B.S.; Analysis or Interpretation: N.B., B.S.; Literature Search: N.B.; Writing: N.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Address for Correspondence/Yazışma Adresi: Nurhilal Büyükkurt, Başkent University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Ankara, Türkiye
E-mail : nurhilalsk@gmail.com ORCID: orcid.org/0000-0002-0895-4787

Received/Geliş tarihi: March 16, 2023
Accepted/Kabul tarihi: May 17, 2023

DOI: 10.4274/tjh.galenos.2023.2023-0109