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Acute Pancreatitis Caused by Bortezomib: Report of one Case and Literature Review

Intissar Lasfar[1*], Hanane Aksim[1], Oualid Hadadia[1], Rachid Akka[1]

[1]Hepato-Gastroenterology Department, Avicenne Hospital, Marrakech

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***Corresponding author:** Intissar Lasfar
Hepato-Gastroenterology Department, Avicenne Hospital, Marrakech

Abstract **Case Report**

Drug-induced pancreatitis has been rarely reported. Bortezomib is a selective and reversible proteasome inhibitor used for the treatment of patients with multiple myeloma (MM). We describe the case of a patient with multiple myeloma who developed acute pancreatitis after treatment with bortezomib, commonly used in the treatment of this disease. The patient was admitted to the hospital with symptoms of AP. Common etiological factors of AP were all excluded. The patient was later diagnosed as having bortezomib-induced pancreatitis. We reviewed the available medical literature on this topic and found eleven other similar cases.

Keywords: Bortezomib, proteasome inhibitors, drug-induced pancreatitis, Acute pancreatitis, medication pancreatitis.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas linked to self-digestion of the gland by its own enzymes and constitutes a medical-surgical emergency [1].

Although gallstones and alcohol are responsible for more than 80%, medications can also cause acute pancreatitis, but they are a rare cause, as the incidence is estimated to be around 1.4%1,2. But it is much more common in risk groups - in children and patients infected with HIV.

There are more than 120 drugs that have been implicated in the cause of PA with different mechanism of injury reported in the literature [2].

Additionally, the World Health Organization database has listed more than 500 medications that may cause PA as an adverse effect [3]. Among which antitumor drugs occupy a special place.

Bortezomib is a proteasome inhibitor approved by the Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma (MM) in May 2003 [4], which has dramatically changed the treatment and prognosis of patients with multiple myeloma.

Its mechanism of action is based on reversible inhibition of the 26s subunit of the proteasome, thus inhibiting its chymotrypsin activity. This leads to the accumulation of an inhibitor of nuclear factor kappa B (NFκB). Inhibition of this factor decreases the expression of adhesion molecules, as well as growth, survival and angiogenic factors, thereby increasing the number of misfolded proteins promoting apoptosis of malignant cells. [5].

Its most common side effects are hematological toxicity, mainly thrombocytopenia, gastrointestinal toxicity (nausea, vomiting, diarrhea, constipation) and peripheral neuropathy.

Rare side effects include cardiac arrhythmias and acute pancreatitis.

Pancreatitis due to bortezomib is very rare, with an estimated incidence between 0.1 and 2% [6], with only isolated reports in the literature.

CASE REPORT

Here we present the case of a patient with MM, who developed acute pancreatitis (AP) after initiation of bortezomib treatment and review the literature on this topic.

This is a 67-year-old man, with ATCD: T2D on insulin, recently followed by hematology for symptomatic multiple myeloma based on the following elements:

- Clinically: Rib + pelvis pain
- Hematological assessment: Complete blood count: WBC:5.3G/L; hb: 7g/dl; plq: 121000 g/L; smear: Presence of red blood cells in rolls; VS: 135mm at the 1st hour. Myelogram: Diluted marrow invaded to 26% by dystrophic plasma cells
- Biochemical assessment: ProtiDogram: Gamma peak quantified at 80g/l ; On immuno-electrophoresis of serum proteins: IgA kappa ; Urine immunoelectrophoresis: Free kappa: <2.5mg/l, Free lambda:>2.5mg/l, qk/L ratio: 11.1, serum calcium: 96.24mg/l, proteins: 120g/l, urea: 0.97g/l, creat: 47.35mg/l, LDH: 133u/l, B2 micro globulin: 4.29mg/l, CRP: 40mg/l
- Radiological assessment:

Abdominal CT:

Osteolytic tumor process of the lateral arch of the 8th left rib associated with diffuse osteolytic lesions and a small amount of ipsilateral pleural effusion (05 biopsies suggesting a plasmacytoma)

Spinal MRI:

Staged signal abnormalities of the ossuex skeleton with pathological right iliac fracture related to his myeloma disease.

He received treatment with bortezomib at a dose of 1.3 mg/m2 subcutaneously (SC) once a week, bisphosphonates and dexamethasone 40 mg orally once a week.

Four weeks after the start of treatment, the patient presented to the emergency room with a picture of acute transfixing epigastralgia, radiating towards the back, aggravated by food, relieved by the gun dog position, associated with food vomiting. then bilious evolving for 04 days before admission without other digestive or extradigestive signs in a context of apyrexia and asthenia.

The examination on admission found a conscious patient, hemodynamically and respiratory stable, afebrile, generalized mucocutaneous pallor, Presence of signs of dehydration and malnutrition, Epigastric tenderness without defense or contracture, no organomegaly, no mass abdominal, presence of pain in the thoracolumbar spinous processes.

The Biological Assessment Found

Blood count: WBC at 11100/ml (PNN: 7490; lympho 2170) hemoglobin 7.6g/dL normochromic lacrocytic; platelets 58,000/ml;

TP 78%; INR: 1.20

Blood Smear:

The leukocyte formula controlled on blood smear shows the presence of some PNN with hypersegmented nuclei. Absence of young or atypical cells with absence of circular plasma cells.

Presence of erythrocyte anisopoikilocytosis with numerous macroovolytes

Absence of platelet aggregates and absence of macroplatelets.

NA: 139; k:3.4; urea; 1.4g/l; creat: 61.84 mg/l; CRP: 25 albumin: 30 g/l; blood glucose: 3.4g/l with negative acetonuria, ASAT: 27; ALT: 23; GGT: 64 U/l; PAL:98 u/l; BT: 9.4; BC:4.5; lipasemia: 500 (6.4N), serum calcium: 96.24; triglycerides: 2.51; CA19-9: <2.06

Viral serology (HVB/HVC/CMV/EBV/HSV) negative, IgG4: Normal

Abdominal CT: In favor of acute Balthazar stage C pancreatitis without dilatation of the intra or extrahepatic bile ducts

The patient's symptoms, clinical, biological and radiological findings were consistent with acute pancreatitis. The most common causes were excluded, in particular biliary, alcoholic, tumoral, metabolic and autoimmune origin, and it was therefore decided that it was an acute pancreatitis of drug origin with an adverse effect associated with bortezomib.

Therapeutically, the patient was placed on food cessation, rehydration, hyperglycemia correction regimen, analgesics and antiemetics on demand, with improvement in the patient's clinical condition and normalization of pancreatic enzymes.

One week later, it was decided to resume chemotherapy with reduced doses of bortezomib (1 mg/m2) and strict monitoring of pancreatic enzymes. No laboratory abnormalities were reported after administration of bortezomib, and the decision was therefore to continue treatment with a reduced dose.

DISCUSSION

The diagnosis of acute pancreatitis requires two of the following criteria: (1) characteristic pancreatic-like abdominal pain, (2) an increase in lipase three times

above the normal value, and (3) findings characteristic of a acute pancreatitis on CT scan.

Although pancreatitis secondary to medications is still considered a rare side effect, most studies conclude that it is the third most common cause after gallstones and alcohol consumption [7].

Bortezomib pancreatitis is a rare but potentially serious complication [8], so it is important to consider it in patients receiving this treatment. The diagnosis is based on the exclusion of the most common causes of pancreatitis [9,1 0].

In our patient, there was no trace of gallstones. Serum calcium and triglyceride values were normal. There was no history of alcohol consumption and no family history of pancreatitis. The patient was not receiving any medication other than bortezomib and dexamethasone.

To our knowledge, there are 11 published cases of bortezomib-induced acute pancreatitis.

We have summarized the main clinical characteristics of these cases in Table 1.

Table 1

Case	Age	Sexe	dose	Onset of symptomes after drugs exposure	Time to resolution of symptome	Reference
1	67	M	1,3mg/m²SC once a week	04 weeks	03 days	Our case
2	58	M	1,3mg/m²IV daYs 1,4,8,11	6 days	1 week	[11]
3	78	M	IV, details n/a	01 month	18 days	[12]
4	67	M	IV, details n/a	04 days	03 days	[13]
5	47	M	IV, details n/a	11 days	02 days	[14]
6	72	F	1,3mg/m²IV daYs 1,4,8,11	01 month	n/a	[15]
7	58	F	1,3mg/m²IV daYs 1,4,8,11	1,5 month	Few days	[16]
8	64	F	1,3mg/m²IV daYs 1,4,8,11	06 days	10 days	[17]
9	67	M	1,3mg/m²SC once a week	04 weeks	11 days	[18]
10	58	M	1,3mg/m²IV daYs 1,4,8,11	04 days after the second cycle	15 days	[19]
11	63	F	1,3mg/m²IV daYs 1,4,8,11	03 days	10 days	[19]
12	67	M	1,3mg/m²SC once a week	01 month	11 days	[20]

The first case was reported by Elouni *et al.*, [11].

Another case of acute pancreatitis in a 17-year-old girl with acute lymphoblastic leukemia treated with bortezomib was not included because she also received L-asparaginase, a chemotherapeutic agent well known to cause acute pancreatitis. Other additional cases may have been missed if pancreatic enzymes or abdominal imaging were not performed.

In all cases reported in the literature, just like our patient, alterations in pancreatic enzymes occurred a few days or even a month after administration of bortezomib.

Regarding the results of abdominal CT scans performed in some patients, some were normal6, or they revealed an edematous pancreas with irregular contours with infiltration of peripancreatic fat.

In our case, the abominal abdominal CT performed in our patient revealed acute pancreatitis Stzde C de Balthazar as in Tevfic and Erica.

The pathophysiology of this complication is unknown. Proposed mechanisms include a direct toxic effect on pancreatic cells or an allergic/immunological response to the drug [21, 22]. Recently, a limited number of studies have shown evidence of the beneficial effect of bortezomib on PA [23, 24].

In one study, the anti-inflammatory effect of bortezomib was reported in experimental acute pancreatitis [23]. In the other study, bortezomib was shown to be able to reduce the severity of AP in mice [24]. But these studies are not enough to obtain definitive results in humans. However, there are no clinical studies on this beneficial effect of bortezomib in PA in humans.

The management of acute pancreatitis induced by was the same for all patients cited in the literature, as our patient requiring cessation of the causative agent and food, rehydration, administration of analgesics and antiemetics on demand. The evolution was favorable for all published cases, the symptoms always disappeared within a few days, and no deaths were observed.

Regarding the resumption of bortezomib, the decision in some patients was to resume treatment at a dose reduced to 1 mg/m². Although a slight increase in pancreatic enzymes was observed at this dose, patients did not develop any symptoms and were able to continue and complete the treatment.

Only half of the other cases reported in the literature restarted bortezomib, but this was at the same initial dose and all had to stop treatment due to recurrence of symptoms.

In our case, treatment with bortezomib was resumed in our patient at a reduced dose of 1 mg/m². No clinical symptoms have been reported with normalization of pancreatic enzymes.

CONCLUSION

Bortezomib pancreatitis is a rare but potentially serious complication4, so it is important to consider this in patients receiving this treatment.

We present these cases to illustrate how we managed this complication and to show that it is possible to continue bortezomib treatment with dose adjustment and frequent monitoring of pancreatic enzymes.

Conflicts of Interest: The authors declare no conflicts of interest.

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