Acute Pancreatitis Following VAD Chemotherapy Combination Consisting Of Vincristine, Doxorubicin, And Dexamethasone In A Newly Diagnosed Multiple Myeloma Patient: A Case Report.

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Abstract

Background/Aims: The frequency of drug-related gastrointestinal adverse effects, including pancreatitis, has increased with the development and use of chemotherapeutic agents. Methods: In our country, a combination of vincristine, doxorubicin, and dexamethasone is frequently used as the first line of therapy in newly diagnosed multiple myeloma. A case with acute pancreatitis that we believe to depend on this therapy is presented. Results: In this case, after treatment of the acute pancreatitis episode in a very dynamic process, a proteasome inhibitor and following high dose chemotherapy with melphalan were used for the primary disease. Currently the patient is under follow-up at remission. Conclusion: It is important to consider chemotherapeutic agents as a possible etiology for acute pancreatitis in patients presenting with gastrointestinal symptoms, even after a few exposures to the agent.

INTRODUCTION

Acute pancreatitis has a serious course with high morbidity and mortality rates (1). Its occurrence as a result of drugs is relatively rare (2). Currently, although the mechanism of drug-related pancreatitis is not completely understood, various hypotheses have been proposed: accumulation of toxic metabolites, hypersensitivity of the body to the drug, and metabolic changes triggered by the drug such as hypertriglyceridemia can be counted among these (1). Multiple myeloma (MM) is a hematological malignancy with increased plasma cells in the bone marrow and frequently associated bone destruction. In treatment, one of the first line combinations is VAD chemotherapy consisting of vincristine, doxorubicin, and dexamethasone. Thus we decided to present this case report in which we believe that the acute pancreatitis was successfully followed up and treated in a very dynamic process due to the start of VAD chemotherapy as the patient was newly diagnosed as MM.

CASE REPORT

A 64-year-old female patient arrived at our outpatient clinic with generalized bodily pain, especially severe at the right hip, fatigue and intermittent fever. Her general condition was bad and review of her systems revealed that 3 months ago she had gone to another medical center with these same complaints and was operated on when laboratory work-up showed a pathological fracture at the proximal side of her right femur (femur neck). Sampling was performed from the operation site and reported the presence of non-specific, plasmocyte-like cells. As her pain increased the following week, she again had gone to that medical center with the following laboratory results: hypoalbuminemia (Albumin: 2.2 gr/dl) and anemia (Hemoglobin: 5.9 gr/dl), along with high erythrocyte sedimentation rate (ESR) (140 mm/h), leading to her hospitalization. Laboratory investigation revealed high serum IgA (2210 mg/dl) and serum kappa (787 mg/dl) and urinary kappa (39.46 mg/dl) levels. Thus, the patient was referred to our outpatient clinic for further

evaluation. Patient history was unremarkable. Her performance status was ECOG 2-3 when she was admitted to our clinic. She had significant constitutional complaints and in her physical examination, no organomegaly, lymphadenopathy, or other positive finding could be determined other than the scar belonging to the past operation and signs of severe anemia (generalized mucosa and conjunctiva paleness, tachycardia). In her first laboratory analyses, blood urea nitrogen (BUN) (67 mg/dl), creatinine (2.32 mg/dl), ESR (123 mm/h), lactate dehydrogenase (LDH) (326 U/L), ferritin (931 ng/ml), uric acid (10.7 mg/dl), and total protein (8.62 g/dl) levels were high while albumin (2.39 g/dl) and hemoglobin (8.26 g/dl) levels were low, alkaline phosphatase (112 U/L), gamma glutamyl transferase (GGT) (44 U/L), and calcium (corrected 8.9 mg/dL) levels were normal, along with the roll formation in her peripheral smear. Spot urinalysis revealed 75 mg/dl protein, while beta 2 microglobulin (11.33 mg/L) and serum IgA (20.2 g/L) levels were markedly increased. The echocardiogram showed the ejection fraction to be between normal limits. After the above-mentioned operation, as the patient was immobile at both home and our center, prophylactic low molecular weight heparin was performed subcutaneously, starting from her first day of hospitalization. In accordance with her nephrology consultation, upper abdominal and bilateral renal doppler ultrasounds were performed and both revealed normal images of the liver, intra-extrahepatic bile ducts, gallbladder, pancreas and vessels. Bone marrow aspiration biopsy and serum and urinary immune fixation electrophoresis revealed IgA/kappa (grade IIIB) MM and after the necessary preparations, VAD chemotherapy protocol consisting of vincristine (0,4 mg/day, continuous iv infusion, 4 days), doxorubicin (9 mg/m2/day, continuous iv infusion, 4 days), and dexamethasone (40 mg/day, iv short infusion, 4 days) commenced. Abdominal pain started on the first day of treatment and, abdominal computerized tomography (CT) was performed to detect probable urinary stones. It was revealed that, besides the lytic lesions in accordance with MM involvement in all bones examined, there were increased densities in accordance with minimal edema-inflammation at the peripancreatic lipoid tissue at the pancreatic tail and in case of clinic suspicion; this finding could suggest acute pancreatitis. However, the abdominal pain was not so intense and was evident especially at the back, thus the patientâ™s vital functions were more closely monitored and lumbosacral magnetic resonance imaging (MRI) was performed to determine whether or not the pain originated from the lumbosacral vertebrae. MRI revealed mass lesions at thoracic 11-12 vertebrae level and at the left side of the sacrum, along with compression fractures at thoracic 12 and lumbar 1st vertebrae corpuses. The patient was evaluated by the Neurosurgical Department, and it was decided to postpone the surgical procedure for the time of remission following chemotherapy. The next day, shortness of breath developed and the Pulmonary Diseases Department suggested performing thorax CT and pulmonary CT angiography with the prediagnosis of pulmonary thromboembolism (PTE). These tests showed that the pulmonary system was patent so the prophylactic low molecular weight heparin was increased to the treatment dose. As the abdominal pain continued increasing and as the serum amylase level was high (8448 IU/L), acute pancreatitis was thought and oral nutrition was stopped. Treatment with imipenem (4x500 mg/day, IV) was started empirically as her fever exceeded 38ÂºC. Her BISAP score was 3 (3). In blood culture, methicillin-sensitive coagulase-negative staphylococci grew so teicoplanin was started at 2x400 mg IV as a booster dose and 1x400 mg IV for maintenance treatment. The patient regularly consulted with the Gastroenterology Department during her chemotherapy and her consistently high pancreatic enzyme levels suggested complicated inflammation. After completion of the first cycle of VAD chemotherapy, control CT was performed and revealed that the pancreatitis had regressed. In the following days, the clinical picture improved, the pancreatic enzyme levels decreased, and her fever was controlled. A magnetic resonance cholangiopancreatography (MRCP) was performed with the aim of illuminating etiology. The patient had a normal pancreaticobiliary tree on MRCP. The patientâ™s general condition was improved, so she was discharged with scheduled control visits. She came back for her first visit at the time of her second chemotherapy; the patient consulted with Gastroenterology as her cholestatic enzymes and serum amylase levels were high (2612 IU/L), and it was decided that the chemotherapy should be postponed as it could lead to a new pancreatitis episode on the basis of her laboratory findings. One month after this, her serum amylase and cholestatic enzyme levels had decreased but were still not within the normal limits. However, the possible risks of delaying MM treatment led to the decision to continue with another treatment protocol less risky in terms of pancreatitis. A combined chemotherapy protocol consisting of bortezomib (1.3 mg/m2/day x 4 days/21 days) and dexamethasone (40 mg/day x 8 days/21 days) was started. The first cycle was completed

uneventfully, and the patient had no complaints when she returned for her second cycle. Blood biochemistry, including serum amylase (104 IU/L), was within normal limits. Thus the second cycle of bortezomib/dexamethasone chemotherapy protocol was given. Evaluations showed that a complete response was obtained so the Neurosurgery Department performed the multiple vertebroplasty operation that they had postponed before due to acute pancreatitis. After this, one more cycle of chemotherapy was performed and, following necessary preparations, high dose chemotherapy was given with the support of autologous hematopoietic stem cell transplantation. The patient had no problems regarding pancreatitis or her primary disease during this process and is currently under follow-up at remission.

DISCUSSION

It is a known fact that gallstones and excessive alcohol consumption account for approximately 70-80% of acute pancreatitis cases (2). Apart from this, autoimmune diseases, iatrogenic events, inflammatory bowel diseases, infections, congenital diseases, neoplasia, structural abnormalities, toxins, trauma, and ischemia are other reasons that are discussed in the etiology. Acute pancreatitis caused by drug use is evidently rare and furthermore, acute pancreatitis triggered by chemotherapeutics is rarer. In the literature, reports incriminating mostly L-asparaginase and cytarabine are striking (4). Acute pancreatitis cases related to alemtuzumab, tamoxifen, vinorelbine, oxaliplatin, and methotrexate have also been reported, though less frequently (5).

In our patient, the acute pancreatitis developed on the first day of the administration of chemotherapy, and resolved within a few days after discontinuation of the drugs. All other possible factors, such as alcohol use history, gallstones, hypercalcemia, hyperlipidemia, and family history were eliminated by means of physical examination, blood chemistry tests and radio diagnostic imaging modalities.

Among the agents used in the present case, dexamethasone may be the first one to blame. Interestingly, there are several reports stating that steroid use in the treatment of disease leads to acute pancreatitis. A good example of this is the acute pancreatitis following pulse steroid treatment in autoimmune bullous disease (6). Some investigators suggest that the main reason for this is the effect of steroids increasing the synthesis of triglycerides. However, some other investigators stated that use of steroids leads to inconclusive results, especially in animal experiments (7). Some authors maintain that in cases where steroid use leads to acute pancreatitis, there always is a different etiological reason (6). In one of the most extensive reviews in recent years, the classification based on published case reports showed dexamethasone as class Ib, being in the second highest risk group (8). However, the general view is that, as steroids inhibit the development of inflammatory mediators and induct apoptosis in pancreatic acinar cells, they have a role in the treatment of acute pancreatitis (9).

On the other hand, doxorubicin is an antineoplastic agent that is more rarely blamed for acute pancreatitis (5). In another classification based on number of published case reports, it is in the lowest risk group (5, 8). Although acute pancreatitis has been reported with protocols combining its liposomal form with other agents, in general doxorubicin alone has never been blamed.

Vinca alkaloids are mostly used together with L-asparaginase, thus they are more frequently connected with acute pancreatitis (7). In two large reviews, however, vincristine and vinblastine have been classified in the last class as the lowest list group in terms of triggering acute pancreatitis alone (5,8). In the literature, acute pancreatitis related to vinblastine has been reported in two cases with germ cell tumors (4). Nevertheless, animal studies have demonstrated that vincristine lead to severe structural damage in mouse pancreas (7).

Some mechanisms have been proposed for drug dependent pancreatitis. Among these, the most supported view is hypersensitivity (10). According to this, acute pancreatitis can develop in hours to days following drug use. This mechanism is not dose dependent and its examples include 6-mercaptopurine, azathioprine, aminosalicylates, metronidazole, and tetracycline (10). This pathway should be kept in mind for our patient.

Another mechanism is the claim that accumulation of toxic metabolites lead to acute pancreatitis. In this mechanism, acute pancreatitis develops a few months after the drug use. An example of this is valproic acid. Thiazides triggering hypertriglyceridemia, tamoxifen, and steroids can also be included in this group.

Another relatively rare pattern observed is when dose dependent, high dose and long-term use of some drugs, mainly erythromycin and acetaminophen, lead to acute

pancreatitis. The general opinion suggests making use of some measures while deciding on the risk of some drugs triggering acute pancreatitis. Some examples are as follows: the pancreatitis should be seen during the use of drug, the absence of other strong reasons that can lead to pancreatitis, the regression of pancreatitis or at least halting of its progression when the drug is stopped, and development of pancreatitis when the drug is started again.

In general, there is no differential clinic finding of pancreatitis triggered by drugs (8). While taking patient history, careful interrogation regarding drug history and the presence drugs classified in high-risk groups can aid the diagnosis. The mechanism of drugs triggering the picture is also important. For instance, in a few weeks time an event that is dominated by an immunological mechanism is going to develop and in this process, detecting possible rushes and eosinophilia will facilitate the diagnosis. However, with long term use of drugs like pentamidine or valproic acid, as the pancreatitis can be seen months after the drug is started, the importance of the accumulation of toxic metabolites of these drugs can be neglected. Nonetheless, in the literature there is no drug reported to lead to acute pancreatitis years after its use.

One of the most important points regarding treatment is the length of use of suspected drug(s). Stopping use of the suspected drug in the early term and starting supportive treatment immediately will be lifesaving. However, another important point that should be kept in mind is drug-dependent pancreatitis is generally in mild to moderate in severity and self-limiting (10, 11). Although deaths have been reported in some publications, prognosis is generally good. Although use of steroids has been suggested in treatment, in the present case, we believe that combined use of steroids, vincristine, and doxorubicin lead to the acute pancreatitis episode. The low molecular weight heparin started on the day the patient was hospitalized and continued in treatment dose as the shortness of breath suggested possible PTE can also play a positive role in the treatment of acute pancreatitis (12). Bortezomib is a proteasome inhibitor that experimental studies have suggested using for the treatment of acute pancreatitis for its anti-inflammatory effect, and in the present patient, it was given almost one month after the clinical picture regressed, as we believe that this agent did not have the potential to trigger acute pancreatitis. As expected, no adverse effect was observed (13). In the period during which dexamethasone was added to bortezomib, the patient was closely followed in terms of a new acute episode but both her clinical status and her enzyme levels were stable. After 3 cycles of bortezomib/dexamethasone treatment, high dose chemotherapy with melphalan was performed with the support of autologous hematopoietic stem cell transplantation. During this process no acute pancreatitis episode was observed.

As a result, in the present case report an acute pancreatitis episode that developed with a high degree of probability, as a result of VAD combination chemotherapy which is frequently started as a first line therapy under the conditions of our country is successfully overcome without any complications, with close follow-up and treatment, along with the completion of required treatment for the primary disease and currently the patient is followed-up under

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