CHEMO-RADIATION THERAPY FOR LOCALLY ADVANCED RECTAL CANCER IN A PATIENT AFFECTED BY HEREDITARY ANGIOEDEMA. A CASE REPORT AND A LITERATURE REVIEW


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ABSTRACT

Angioedema is a rare disorder caused by C1 inhibitor deficiency that may be either hereditary or acquired. We report a case about a 42-year-old male who was referred to our Centre of Radiotherapy with the diagnosis of a locally advanced rectal carcinoma and Hereditary Angioedema. Preoperative chemo-radiotherapy was proposed during our gastro-enteric tumour board and the rheumatologist gave no absolute contraindication to chemo-radiotherapy ensuring that the patient was instructed to control angioedema attacks by self-administering C1 inhibitor concentrate. A Total Fractionated Dose of 54 Gy was delivered to the target volume (45 Gy to the whole pelvis and a boost dose of 9 Gy to the rectal volume only) with 1.8 Gy daily fractions, in association with continual infusion of 5-fluorouracil (300 mg/mq) five days per week. The treatment was well tolerated; the patient presented only G1 gastrointestinal toxicity according to RTOG/EORTC score criteria with no angioedema attacks during treatment. Severe abdominal cramps, associated with bowel sounds, diffuse abdominal pain and nausea were referred by the patient a week after completion of treatment. Complete symptom remission appeared after self-administering C1 inhibitor concentrate. To our knowledge, this is the only patient described in literature who completed chemo-radiotherapy in the presence of a life threatening condition such as Hereditary Angioedema. It is interesting to notice that even though no data exist about the use of radiotherapy on the pelvis in patients affected by Hereditary Angioedema this treatment modality seems to be safe even when associated with chemotherapy.

Key words: Hereditary Angioedema, Rectal Cancer, Chemo-radiotherapy, Gastro-intestinal toxicity.

Received May 18, 2014; Accepted September 02, 2014

Introduction

Angioedema caused by C1 inhibitor deficiency is a rare disorder that may be either hereditary or acquired, the latter being mainly associated with lymphoproliferative disorders[1]. Hereditary angioedema (HAE) is an autosomal-dominant deficiency of C1 inhibitor (a serpin inhibitor of kallikrein, C1r, C1s, factor XII, and plasmin). Quantitative or qualitative deficiency of C1 inhibitor leads to the generation of vasoactive mediators, most likely Bradykinin. The clinical syndrome consists in repeated bouts of non-pruritic edema of the face, larynx, extremities, and intestinal viscera. Hereditary angioedema is often misdiagnosed and poorly treated; diagnosis requires careful medical and family history and the measurement of functional C1 inhibitor and C4 levels. Attenuated androgens, anti-fibrinolytics, and C1 inhibitor concentrate (C1INH) are used for long-term and pre-procedure prophylaxis, but have significant drawbacks. C1 inhibitor concentrate and fresh frozen plasma are available for acute intervention[2]. Limited experience is reported in literature about the association between this syndrome and malignant tumors requiring aggressive treatments with relevant side effects. Our aim is to report about a patient who underwent chemo-radiotherapy treatment (CHT-RT) for a locally advanced rectal carcinoma in the presence of HAE. This is to contribute to a better knowledge of the possibility to safely treat these patients affected by life-threatening pathologies.
Case presentation

We report about the case of a 42-year-old male who was referred to our Centre of Radiotherapy with the diagnosis of a rectal carcinoma and Hereditary Angioedema (HAE) which was diagnosed when he was 12. His past medical history was significant for asthma, hypertension, left varicocele and hydrocele. In October 2012 he presented intermittent rectal bleeding and in March 2013 he underwent colonoscopy demonstrating an ulcerated, exophytic rectal lesion, pathology showing an adenocarcinoma. A lesion at 1 cm from the anal verge extending cranio-caudally for 10 cm and infiltrating all mucosal layers, reaching the perivisceral fat with small perirectal nodes was demonstrated on rectal ultrasound-endoscopy. Loco-regional staging was usT3 N+. No distant metastases were detected at total body computed tomography (CT).

Preoperative CHT-RT was proposed during our gastro-enteric tumour board; the rheumatologist following the patient was involved and gave no absolute contraindication to CHT-RT ensuring that the patient was instructed to control any angioedema attack by self-administering C1INH. Prophylaxis with androgens and/or tranexamic acid was also suggested. The risks related to the chemoradiation therapy treatment were widely explained to the patient who accepted and signed a written consent form. He underwent a planning CT scan (GE LightSpeed® Scanner, GE Healthcare Diagnostic Imaging Slough, UK) of the abdomen and pelvis region in prone position at 5 mm thickness and the images were transferred to the Precise Plan Treatment Planning System (Elekta Oncology Systems, Crawley, UK) where Clinical Target Volume (CTV) and organs at risk (OAR) were defined. CTV was delineated as the rectal lesion including pelvic nodes. OAR were bladder, bowel and femoral heads. Planning Target Volume (PTV) was obtained adding 5 mm all around the CTV. A Total Fractionated Dose of 54 Gy was delivered to the target volume (45 Gy to the whole pelvis and a boost dose of 9 Gy to the rectal volume only) with 1.8 Gy daily fractions. High energy photons (10 and 15 MV) were used to deliver, 5 days per week, the prescribed dose using a commercial Linac (Standard Elekta Precise®) in association with continuous infusion of 5-Fluorouracile (5-FU) (300 mg/mq). The treatment was well tolerated, blood samples were obtained regularly during treatment and resulted unremarkable; the patient presented only G1 gastrointestinal toxicity according to RTOG/EORTC toxicity criteria score with no angioedema attacks during treatment. Severe abdominal cramps, associated with bowel sounds, diffuse abdominal pain and nausea were referred by the patient a week after completion of CHT-RT treatment disappearing after self-administering C1INH with complete symptom remission.

A CT scan and a rectal ultrasound endoscopy were obtained showing a considerable downsizing in spite of the fact that ultra-sound staging didn’t change (uT3 uN-).

Eight weeks after the end of chemo-radiation the patient underwent surgery with total mesorectal excision (TME) and pathology demonstrated a poorly differentiated adenocarcinoma of the rectum with mucinous aspects. Final stage was ypT3 ypN0 G3. Eight cycles of chemotherapy using Oxaliplatin, 5-FU and folinic acid were administered postoperatively. Patient is disease free one year after completion of treatment.

Discussion

Literature reports only few cases of patients affected by angioedema and treated for a neoplasm and, to our knowledge, only one case affected by HAE and treated with concurrent CHT-RT for cancer by Kasamatsu et al. in Japan. They reported about a 69-year-old man affected by HAE and lung cancer who developed acute attacks of angioedema during chemotherapy. Attacks were managed by self-administration of C1INH and for this reason danazol was given during concurrent CHT-RT preventing further occurrence of angioedema attacks\(^3\).

Christie D.R.H. et al.\(^4\) described the association between HAE and breast cancer in a family in which diseases coexisted. Only a member of this family underwent surgery followed by adjuvant chemotherapy. She was given a course of radiation therapy in association with danazol without developing severe reactions or any angioedema attack.

The association of rectal carcinoma and Acquired Angioedema (AAE) has been described by Cohen et al.\(^5\). The patient was treated with danazol, he underwent surgery and developed only one episode of laryngeal edema after surgery. He was negative for local recurrence or distant metastases at follow-up.

In spite of the lack of correlation between HAE and cancer, an association between AAE and immunoproliferative disorders (non Hodgkin’s lym-
phoma and Chronic Lymphocytic Leukaemia) has been described.

As few data exist in literature about concurrent diagnosis of HAE with a tumour requiring concomitant CHT-RT no specific conclusions about safety of these associated treatments have been stated.

To our knowledge this is the only patient recently described in literature and treated with concomitant CHT-RT for locally advanced rectal carcinoma with an associated diagnosis of HAE.

As HAE represents a potentially life threatening clinical condition characterized by acute and unexpected onset of symptoms caused by different kind of triggers, we were concerned about the possibility to safely deliver our treatment in the presence of such a situation. One of our main concern was that the patient was alone in the treatment room. In the case of an angioedema attack occurring during treatment delivery he could not move. A latent period of about 20-30 seconds is necessary to give access to the treatment room to give medication to the patient and this represents an obstacle in case of an emergency. Moreover, we instructed the patient about the danger related to movement during treatment for radioprotection safety.

Another point of concern was the fact that most of the symptoms of HAE are gastrointestinal disorders that may be relevant when undergoing radiotherapy on the pelvis, especially when it is associated with a phase-specific anti-metabolite like 5-FU, which presents gastrointestinal toxicity as the most frequent side effect"). For this reason, in order to further decrease radiation therapy-related adverse effects, we instructed the patient to follow a diet regimen which we recommend to all of the patients undergoing treatments on the abdomen and pelvis.

Following all these recommendations and instructions the patient completed the treatment without toxicity related to CHT-RT. It is remarkable that during the course of irradiation he did not develop any angioedema attack reporting only an episode of severe abdominal cramps, bowel sounds and nausea occurring a week after the end of treatment.

We report this limited experience of us in the treatment of a severe pathology as a locally advanced rectal tumour is in the presence of a life threatening condition like HAE. This is to testify that an internationally accepted protocol as preoperative CHT-RT treatment for locally advanced rectal cancer may be safely delivered at least in patients affected by HAE. Due to this limited experience we cannot comment on the possibility to extend these conclusions to all of the patients with such a diagnosis including those with the acquired form which seems to be more common.

References


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