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The use of radiotherapy in Hereditary Angioedema Type 1- C1 Inhibitor deficiency

(Uso de radioterapia en Angioedema hereditario por déficit de C1 inhibidor tipo I)

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Abstract (english)

We present a clinical case of a 72 year old man with Hereditary Angioedema Type 1. It´s a rare, potentially fatal disease, especially due to causing episodes of laryngeal angioedema. He has a past medical history of lip squamous-cell skin cancer, which is currently relapsing, with lateral margins of the surgical resection affected requiring treatment with local radiotherapy. He was referred to our Allergology Unit from the Dermatology and Radiotherapy Unit, because this procedure could trigger an angioedema attack. Few publications exist which associate C1-INH-HAE with malignant tumours that require aggressive treatments. We recommended a short term prophylaxis with Stanozolol, increasing the usual dose which is used for maintenance, instead of purified plasma concentrate of C1 esterase inhibitor, which is the preferred treatment in countries where it can be afforded, due to its significant cost and because the patient had enough time to take attenuated androgens for 5 days before the procedure according to the guides. We are describing the first case of treatment with facial radiotherapy in the presence of a potentially mortal illness, C1-INH-HAE Type I..

Keywords (english)

Hereditary Angioedema Type 1 due to C1 esterase inhibitor deficiency. Squamous cell lip Carcinoma. Radiotherapy.

Resumen (español)

Presentamos un caso clínico de un varón de 72 años con Angioedema hereditario por déficit de C1 inhibidor tipo I con antecedente personal de Carcinoma espinocelular de labio inferior intervenido en 2010 que cuatro años después recidiva sobre el lecho tumoral con márgenes laterales de la resección quirúrgica afectos precisando tratamiento adyuvante con radioterapia local. Este procedimiento podría desencadenar un ataque agudo. Se administraron un total de 20 sesiones de 55 Gy a 2.75 Gy/fracción, sobre cicatriz de labio inferior, usando como profilaxis preprocedimiento estanozolol, siendo bien toleradas sin presentar ataques de angioedema durante el tratamiento. Recomendamos profilaxis a corto plazo con estanozolol, aumentando la dosis habitual que el paciente realizaba de mantenimiento, en lugar de concentrado plasmático purificado de inhibidor de la C1 esterasa humano, a pesar de ser el tratamiento de elección para la profilaxis preprocedimiento en los países donde se encuentra disponible, debido a su elevado coste y porque el paciente tuvo tiempo suficiente para comenzar el aumento de dosis de andrógenos atenuados los 5 días previo al procedimiento de acuerdo con las guías. Describimos el primer caso de tratamiento con radioterapia facial en un paciente con Angioedema hereditario por déficit de C1 inhibidor, tratado eficazmente con andrógenos atenuados como profilaxis preprocedimiento evitando los

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costes sanitarios que conlleva el tratamiento de elección, siendo una buena opción terapéutica en estos pacientes cuando requieren procedimientos que pudieran desencadenar ataques agudos así como en aquellos países en los que no se encuentra disponible el tratamiento de elección.

Palabras clave (español)

Angioedema hereditario por déficit de C1 inhibidor tipo I. Carcinoma espinocelular de labio. Radioterapia.

Introduction

A clinical body considers Hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) to be a rare, potentially fatal disease, especially due to causing episodes of laryngeal angioedema. Various phenotypes have been described; Type I and Type II. Type I is characterised as the quantitative drop in plasma levels of the C1 esterase inhibitor protein. With regards to Type II, the levels of the inhibitors of the C1 esterase inhibitor are normal, but there is a reduction in functional activity. Both are due to mutations in the SERPING1 gene, with more than 300 described in literature [1]. It´s prevalence is unknown, Roche's reference states a minimal prevalence of 1.09/100.00 inhabitants in Spain [2].

In many cases is underdiagnosedillness. Correct diagnosis of C1-INH-HAE enables us to establish an adequate treatment of the illness, with the objective to prevent death and reduce the morbidity rate.

The treatment is based on four pillars [1,3]:

1. Secondary prevention is based on eliminating possible precipitant attacks, such as infectious processes, microtraumatisms, psychological and emotional stress and avoiding medicines that increase the frequency and severity of the angioedema attacks (angiotensin converting enzyme inhibitors, estrogens and dipeptidyl peptidase inhibitors, gliptins).

2. Long term prophylaxis. There are 3 groups of medicines for treatment and maintenance:

Danazol and Stanozolol are the fundamental attenuated androgens that are used to treat C1-INH-HAE. They are more efficient than other androgens and have fewer side effects [4]. Their use is not indicated for children, pregnant women, women who have previously suffered from breast cancer, men with breast or prostate cancer, patients with nephrotic syndrome or those with significant alterations of hepatic function.

Antifibrinolytics available include aminocaproic acid and tranexamic acid, it's cyclical derivative. Their use can be reserved for those patients who have contra-indications or who don't tolerate the first line options.

The replacement treatment with plasma purified concentrate of C1 esterase inhibitor is indicated for patients uncontrolled with high doses of oral treatment, or those that present with side effects or have contraindications to use the previous options.

3. Short term prophylaxis, it´s used before a medical or surgical procedure to prevent triggering attacks of angioedema.

Amongst the different drugs available, there is the purified plasma concentrate of C1 esterase inhibitor, which is the preferred treatment in countries where it can be afforded, given its significant cost. The attenuated androgens can be used when the risk of intervention is considered low, there is enough time to take them for 5 days before the procedure and when the above treatment is not available. Antifibrinolytics and fresh frozen plasma is only recommended in cases where none of the above treatments are available.

4. The treatment of the acute attacks should be prompt. Currently there exists five specific drugs. Purified plasma concentrate of C1 human protease inhibitor and the recombinant C1 esterase inhibitor, are both administered intravenously. They act by replacing the deficient C1 inhibitor plasma protein. Icatibant and Ecallantide, are both administered subcutaneously. Lastly, fresh frozen plasma use is limited to when the above treatments are not available.

Of all the drug treatments, plasma purified concentrate of C1 inhibitor and Icatibant are authorised by the European Medication Agency for self-administration, prior to training.

Few publications exist which associate C1-INH-HAE with malignant tumours that require aggressive treatments. Upon reviewing the literature, we found only one case of a man with lung cancer metastasis [5], one with locally advanced rectal carcinoma [6] and in another, a woman with breast cancer [7] treated prophylactically with attenuated androgens (danazol), tolerating surgery, chemotherapy and radiotherapy well.

In the literature there is nothing describing the use of facial radiotherapy for patients with C1-INH-HAE Type I.

Case report

A 72 year old man was diagnosed some years ago with C1-INH-HAE Type I, he is well controlled with long term prophylaxis using attenuated androgens, Stanozolol 2mg/24 hours since 2008. He has a past medical history of lip squamous-cell skin cancer in 2010. He is currently relapsing, with lateral margins of the surgical resection affected requiring treatment with local radiotherapy.

He was referred to our Allergology Unit from the Dermatology and Radiotherapy Unit, because this procedure could trigger an angioedema attack.

Until the moment the patient gets better, carrying out a well controlled treatment and followed up with attenuated androgens, Stanozolol, being submitted to two previous surgical procedures in relation to the lip carcinoma, treated with short term prophylaxis with 1,000 units of the C1 inhibitor being well tolerated.

Before starting radiotherapy treatment, a full blood count, coagulation screen, general biochemistry including a hepatic profile, lipid and alpha-fetoprotein were all requested. A complement study revealed normal levels of C3 103mg/dl (range 82-170), C4 16mg/dl (range 12-36) and C1q 28mg/dl (range 10-25), with the C1 deficiency inhibitor 11mg/dl (range 21-39).

The local radiotherapy complete planned scheme, in the cervicofacial region, included four weeks of treatment with 20 sessions in total of electrons on the tumour bed had a margin of 1cm of 55Gy to 2.75Gy/fraction five days a week.

Due to the long procedure process and the potential triggering of an angioedema attack, we recommended a short term prophylaxis with Stanozolol, maintenance dose was tripled to 2mg every 8 hours. We followed the guidance of treating for 5 days before the start of the radiotherapy, throughout the whole cycle and continuing it for five days after finishing radiotherapy, which was well tolerated without presenting attacks of angioedema throughout procedure.

Discussion

In the written action plan was indicated the administration of Icatibant the cycle of radiotherapy or at home for an acute angioedema attack if required.

Once completed the procedure, the maintenance dose of Stanozolol was used, he was previously well controlled with 2mg every 24 hours.

Physical trauma is a characteristic precipitant and is recognized in patients with C1-INH-HAE. There is a high risk of development of laryngeal angioedema in all diagnostic procedures or therapies that involve to the upper respiratory tract. Angioedema attacks can also be caused by emotional stress or anxiety.

In our patient with C1-INH-HAE Type I, there are differents factors that influence the risk of suffering an acute attack, which include the manipulation to the cervicofacial level, the proximity of mucous membranes, the oncology base of the illness, the psychological stress associated with the procedure and the length of the process.

In the literature there is nothing describing the use of facial radiotherapy for patients with C1-INH-HAE.

Therefore, for this case, it was really important to carry out an efficient prophylaxis, to have a written action plan and a multidisciplinary collaboration.

We recommended a short term prophylaxis with Stanozolol, increasing the usual dose which is used for maintenance, instead of purified plasma concentrate of C1 esterase inhibitor, which is the preferred treatment in countries where it can be afforded, due to its significant cost and because the patient had enough time to take attenuated androgens for 5 days before the procedure according to the guides.

We are describing the first case of treatment with facial radiotherapy in the presence of a potentially mortal illness, C1-INH-HAE Type I.

The patient was able to complete the procedure without causing an angioedema attack.

The short term prophylaxis with attenuated androgens has reduced the costs.

Therefore it could be a therapeutic option for those patients like in our case, especially in those countries where the purified plasma concentrate of the human C1 esterase inhibitor is not available.

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