A rare form of hereditary angioedema could be confused with ovarian cancer

Lidia María Melero-Cortés1,*, María del Rosario Rosso-González1, Javier Frutos-Arenas2, José Manuel Silvan-Alfaro1, María Angeles Martínez-Maestre1

1 Clinical Management Unit of Gynaecology and Breast Pathology, Virgen del Rocío University Hospital, 41013 Seville, Spain
2 Clinical Management Unit of Radiodiagnostic, Virgen del Rocío University Hospital, 41013 Seville, Spain

*Correspondence: lidiam.melero.sspa@juntadeandalucia.es (Lidia María Melero-Cortés)

DOI:10.31083/j.ejgo.2021.02.2164

This is an open access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).
Submitted: 07 June 2020 Revised: 05 August 2020 Accepted: 06 August 2020 Published: 15 April 2021

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent and circumscribed episodes of subcutaneous and submucosal edema involving different organs. Gastrointestinal involvement usually presents as abdominal pain. The presence of ascites is rare with only few cases reported in the literature. We report a case of HAE with ovarian edema, ascites and elevation of CA-125 which led to an initial suspicion of ovarian neoplasia. It is important for gynaecologists to be aware of HAE, as this disease can present a symptomatology similar to that described in gynaecological diseases and therefore lead to unnecessary invasive procedures and delay proper treatment.

Keywords
Hereditary angioedema; C1-inhibitor; Abdominal pain; Ascites; Ovarian edema; Ovarian neoplasia

1. Introduction

Hereditary angioedema (HAE) is a genetic disease, with an incidence of 1: 50,000 individuals, although this may vary in different regions and the exact incidence and prevalence is unknown [1–3]. In its classical form, the fundamental defect of HAE is a deficient or dysfunctional C1 esterase inhibitor (C1-INH), a protease inhibitor in the serpin superfamily.

C1-INH regulates multiple proteases involved in the complement cascade, contact-system, coagulation, and fibrinolytic pathways. Increased production of bradykinin has been postulated as a likely physiological mechanism of the clinical manifestations of angioedema, however the biochemical mechanisms responsible for crises are not accurately known.

Different forms of HAE are currently recognized and genetically identifiable [1, 2, 4]:

i. HAE due to C1-INH deficiency (Type 1 HAE, HAE-1). Is characterized by low antigenic and functional C1-INH levels and accounts for 85% of cases.
ii. HAE due to C1-INH dysfunction (Type 2 HAE, HAE-2). Is characterized by normal (or elevated) antigenic but low functional C1-INH levels. Type 2 HAE accounts for 15% of cases.

HAE-1/2 are autosomal dominant conditions with complete penetrance. These are caused by one of more than 450 different mutations in the SERPING1 gene, which codes for C1-INH. In approximately 20%–25% of patients, a de novo mutation of SERPING1 is responsible for the disease.

In 2000, HAE with normal C1-INH (HAE nC1-INH) was described. The clinical presentation is phenotypically similar to that of HAE-1/2 and has an autosomal dominant inheritance pattern with incomplete penetrance. It occurs mainly in women, and the age of onset is usually after childhood. Identifying patients with HAE nC1-INH is more challenging than identifying those with HAE-1/2 due to the lack of accessible and available assays, including genomic testing for diagnosis. The disorder is classified into subtypes according to the associated genetic mutation: a mutation affecting factor XII (HAE-FXII), angiopoietin-1 (HAE-ANGPT-1), plasminogen (HAE-PLG), or kininogen-1 heavy-chain (HAE-KNG1) [5] or an unknown genetic mutation (HAE-U). HAE-FXII is the most common form of HAE nC1-INH. The mechanisms underlying angioedema in HAE with plasminogen dysfunction, HAE with angiopoietin-1 dysfunction and HAE with kininogen-1 heavy-chain dysfunction are unclear. The majority of patients who have HAE with normal C1-INH levels remain in the unknown-mutation category, for which many potential pathogenic explanations remain to be investigated. At present, the diagnosis of HAE nC1-INH is based on consensus guidelines [6].

HAE is characterized by recurrent episodes of subcutaneous or submucosal edema, usually self-limiting and involving mostly the extremities, face, airway and gastrointestinal tract, although its involvement can be very varied. Pharyngeal and laryngeal locations can be fatal (in up to 30% of cases) if they are not treated correctly. Gastrointestinal involvement, along with intestinal wall edema, leads to abdominal pain crises accompanied at times by nausea and/or emesis. Symptoms related to other locations are rarer (urinary retention, cough, pleural pain, ascites) [7].

Sometimes, its atypical form of presentation leads to misdiagnosis, with the use of ineffective treatments and even un-
necessary surgical intervention. We highlight this situation by reporting the case of a HAE 39-year-old patient with ovarian edema, ascites and elevation of CA-125 which led to an initial suspicion of ovarian neoplasia.

2. Case report

A 39-year-old woman came to the hospital presenting with abdominal pain accompanied by post-prandial abdominal swelling and sometimes the presence of nausea and vomiting.

Since 2014 the patient had been following up in the Angioedema Unit for recurrent episodes of tongue swellings after initiation of oral contraceptives, with lack of response to high-dose antihistamines and corticosteroids. After years of study, genetic testing was requested, with diagnosis of HAE by mutation in the factor XII gene (Exon 7 mutation of F12 gene encoding for factor XII protein: change in exon 7 (in heterozygosis): c530C>T (predictable change in protein: p. Ala177Val.rs144821595)).

The patient’s first pregnancy had been complicated by polyhydramnios, fetal hydrops and secondary maternal anasarca (Mirror syndrome), with satisfactory evolution in the early postpartum.

The patient was currently asymptomatic, with no severe episodes of angioedema for 2 years.

The physical examination highlighted only a distended abdomen, with no tension and diffuse tenderness to palpation. The abdominal ultrasound described the presence of ascites in moderate amount at level peri-hepatic, peri-splenic, in both paracolic gutters, among intestinal loops and in the pelvis.

The abdomino-pelvic computerized tomography (CT) highlighted in all quadrants the presence of ascites in moderate amount, with bilateral adnexal masses left predominance, minimal edema of intestinal walls and thickening of the gastric wall. Further explore these results, gastroscopy was performed without pathological findings. A preliminary diagnosis of a disseminated ovarian tumour was considered and the patient was admitted under the gynaecological oncology team.

Tumor markers were negative with the exception of CA-125 at 472 U/mL (reference values 0–35 U/mL). The blood count, coagulation and biochemistry study, including renal and hepatic function, were normal (Table 1). Transvaginal ultrasound showed a regular contoured uterus with an endometrium of 9.2 mm and both ovaries with an hypechogenic stroma and no abnormal doppler uptake (Fig. 1).

As there were no suggestive signs of peritoneal carcinomatosis, ovarian cancer diagnosis was ruled out. On the basis of the diagnosis of HAE, our patient was treated with Cinryze® (plasma-derived C1 inhibitor) 1000U intravenously in single dose. At 48 hours she experienced a reduction in abdominal pain and the ultrasound showed the resolution of ascites (Fig. 2). Serial ultrasound control was performed checking complete remission of it and negativity for the CA-125 marker.

3. Discussion

HAE is characterized by recurrent episodes of submucosal or subcutaneous edema. Depending on the location of the edema, we can observe the following [1, 7, 8]:

i. Skin: Recurrent nonerythematous, nonpruriginous, circumscribed angioedema, with no temperature increase. Not associated with urticaria.

ii. Gastrointestinal tract: Recurrent colicky abdominal pain (sometimes severe), abdominal distension, nausea, vomiting, constipation or diarrhea, orthostatic hypotension, dehydration and hypovolemic shock.

iii. Upper airway: Feeling of pharyngeal occupation, dysphagia, change of tone of voice, stridor, dyspnoea, pharynx-laryngeal edema, upper airway obstruction and/or asphyxia.

Since it is rare, the condition is often not recognized. Consequently, patients may receive either ineffective treatments for HAE or unnecessary surgery. Although the interval between the onset of symptoms and diagnosis has decreased from earlier reports of approximately 22 years, delays remain unacceptably long at 8 to 10 years [1, 3].

Our patient presented episodes of recurrent pain, without the appearance of visible angioedema, except for ovarian edema which was interpreted as adnexal masses in CT. The presence of enlarged ovaries, ascites and an elevated ovarian tumour marker led to the initial erroneous diagnosis of a malignant nature.

The point of interest in this case, therefore, lies in establishing an adequate differential diagnosis in the face of findings and symptoms often described in gynaecology consultations and an obscure disease, such as HAE, unrecognised among many gynaecologists.

HAE should be included in the differential diagnosis of recurrent abdominal pain, especially if the diagnosis is already known and is also accompanied by peritoneal liquid, which makes it even more likely. Ascites can have several origins, both benign and malignant in nature. In 85% of cases, liver cirrhosis is the main cause. The second cause of ascites in frequency is malignant neoplastic disease that causes peritoneal carcinomatosis, taking in 80% of cases its origin in ovarian, breast, endometrial, colon, stomach, pancreas and bronchial neoplasms.

Krukenberg’s tumour is the term used to refer to gastric adenocarcinoma with ovarian metastases, usually bilateral, ascites and elevation of CA-125. What increased the premises of this being the diagnosis was the thickening of the gastric wall described in CT, ascites, a high value of CA-125 and the initial suspicion of tumour in the ovaries. However, this diagnosis was excluded after a normal result in gastroscopy.

In females of 40 to 60 years of age, the aetiology of malignant ascites are most often ovarian tumours, characterised
by the symptoms of pelvic/abdominal pain, satiety, and abdominal distention. The symptomatology referenced was strongly recognizable within our patient, hence a diagnosis of peritoneal carcinomatosis, secondary to ovarian neoplasia was made. However, although enlarged ovaries were indeed identified upon further assessment using a transvaginal ultrasound, this was congruent with no detection of adnexal tumours, thus preventing the removal of a healthy ovarian stroma as an ovarian oedema was therefore identified. Expert hands, transvaginal and abdominal ultrasound, and a readily accessible diagnostic tool, have the ability to ensure the search for signs compatible with an episode of HAE to guide
Fig. 1. Transvaginal ultrasound. (A) Right ovary with hyperecogenic stroma and anechoic cyst compatible with lutein cyst in resolution. (B,D) Both ovaries without abnormal Doppler uptake. (C) Left ovary with characteristics similar to those described in the right ovary. (E) Uterus with regular contoured and morphology with homogenous endometrium. Moderate amount of fluid in Douglas.

Fig. 2. Abdominal ultrasound. (A,B) Both ovaries with normal eco-structure. (C) Cross-section on the uterine background, where you can see the absence of peritoneal liquid at the pelvic level. (D) Absence of peritoneal liquid at level peri-hepatic.
diagnosis and rule out adnexal pathology, without the need to resort to other invasive processes. Performing a diagnostic laparoscopy was considered, but the surgical risk to this procedure, along with the low probability of explaining the findings and symptomatology as a result of a neoplastic process, caused it to be ruled out without first considering other possible diagnoses.

In patients with known HAE, the presence of ascites should be tilted in favour of a manifestation related to this, especially if it is accompanied by edema of the intestinal wall [1, 7]. Ascites in these cases is caused by extravasation of intravascular fluid into the peritoneal cavity due to edema of the intestinal wall. It has been proposed that ultrasonographic research of the peritoneal cavity can be useful for early diagnosis of HAE, mainly in cases of relapsed abdominal pain [9]. In our case, the complexity to reach a conclusion about this diagnosis may be even greater since cases of HAE nC1-INH abdominal manifestations are less frequent (50% versus 90% described in cases of HAE-1/2) [10]; the patient had not previously exhibited similar manifestations; and was asymptomatic for 2 years without the need for treatment. In addition, during an episode of abdominal swelling, a typical finding is haemoconcentration, due to fluid loss as a result of the increased vascular permeability. Given the inadequate control of the fibrinolytic system, D-dimers may typically be increased during HAE attacks; however, our patient did not present abnormal values.

The resolution of symptomatology following intravenous administration of a C1 inhibitor, as well as the disappearance of peritoneal liquid, showed that both abdominal pain and ascites resulted from a HAE attack.

Given the low specificities, CA-125 and other tumor markers have a low diagnostic value and should only be used in neoplastic disease monitoring. In this case, ascites was probably responsible for elevated serum levels as later demonstrated by its negativity at the resolution of the symptoms.

To the best of our knowledge this is the first case described in the literature of females in which an episode of HAE is accompanied by ovarian edema, ascites and elevation of CA-125 levels.

On the other hand, the Mirror syndrome during pregnancy may have been related to an exacerbation of its pathology, in relation to the high estrogenic serum levels achieved during pregnancy [11, 12].

Finally, we want to emphasize the various ways HAE can be presented, including the ovarian edema. In this context, it’s important to take into account the management of pelvic ultrasound in expert hands for the assessment of possible adnexal pathology, being of crucial importance to differentiate ovarian stromal edema from an ovarian tumour, to prevent patients from undergoing unnecessary surgeries.

4. Conclusions

It is important to recognise the various ways HAE could present, including atypical presentations. This will help us avoid unnecessary invasive procedures and provide a more appropriate therapy. The role of a gynaecologist is important in order to make a correct and early diagnosis and thus avoid iatrogenic manoeuvres and therapeutic delays.

Author contributions

LMC and AMM designed the research study. LMC performed the research. RRG, JFA and JMSA provided help and advice. LMC and AMM wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Virgen Macarena and Virgen del Rocio University Hospitals (approval number: 1529-N-20).

Acknowledgment

We thank Daniel Candela-Martinez and Annabel Meir, for assistance with the support in writing the manuscript.

We would also like to show our gratitude to Carmen Toquero-Pichardo, oncology nurse, for her help during the course of this research.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References


