

Presentation of an extraordinary colic: abdominal pain as the first and only utterance of an acquired C1-inhibitor deficiency

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Accepted 23 September 2022

SUMMARY

C1-inhibitor deficiency is a rare disease which incorporates acute self-limiting intermittent swelling of the subcutaneous tissue and mucous membranes. Attacks most frequently affect the face and/or the upper airway. Isolated angioedema of the small bowel is an uncommon manifestation and often accompanied by diagnostic delay. In the present case, abdominal pain turned out to be the first and only utterance of an acquired C1-inhibitor deficiency, secondary to a splenic marginal zone lymphoma. Imaging showed wall thickening of the small intestine, ascites and splenomegaly. The abdominal pain and intestinal wall thickening with surrounding ascites on imaging spontaneously resolved each episode within 2–3 days. Gastrointestinal manifestations of angioedema may mimic an acute abdomen, and subsequently one-third of these patients undergo unnecessary surgery prior to a definite diagnosis. This emphasises the importance of considering the diagnosis in case of an 'extraordinary colic'.

BACKGROUND

An acquired C1-inhibitor (C1-INH) deficiency, also referred to as acquired angioedema (AAE), is an unusual and rare cause of acute abdominal pain. Angioedema is characterised by acute-onset swelling of the subcutaneous tissue and/or mucous membranes and may manifest itself anywhere in the body. Angioedema typically occurs in the context of an allergic reaction to food, medication or other allergens.¹ In this case, it is mediated by mast cell activation, and clinical presentation is often associated with pruritus and urticaria. In severe cases, it may develop into an anaphylactic shock with life-threatening acute laryngeal oedema. In contrast, angioedema occurring in cases of C1-INH deficiency is a form of bradykinin-mediated angioedema characterised by a lack of pruritus, urticaria and response to antihistamines.² Clinical presentation often includes self-limiting periodical oedema of the facial subcutaneous tissues, the gastrointestinal tract, the oral cavity/larynx, genitalia or extremities.³ The oedema may present site specific or be combined and is self-limiting. A C1-INH deficiency can be hereditary (C1-INH-HAE) due to mutations affecting the SERPING1 gene or acquired (C1-INH-AAE). In the latter case, it occurs frequently secondary to underlying diseases. The exact prevalence of C1-INH-HAE is unknown and varies widely, but is estimated at 1:50 000–1:100

000.^{4 5} AAE is less common than the hereditary form, with an estimated ratio of 1:10 and typically presents in adults.⁶

Here, we describe a patient with recurrent acute abdominal pain based on small bowel angioedema in the context of an acquired C1-INH deficiency, as first presentation of a splenic marginal zone lymphoma (SMZL). Subsequently, the classification, associations and pathophysiology of C1-INH deficiency are discussed.

CASE PRESENTATION

A woman in her 50s presented to our emergency department with acute abdominal colicky pain accompanied by nausea and vomiting. Her medical history contained no relevant diseases. She used no medication, never smoked and used five to eight units of alcohol (two to four medium glasses of wine, 175 mL alcohol by volume 12%) in the weekend. Her family history showed no gastrointestinal diseases.

First general impression showed a painful, pale and clammy patient. Vital parameters contained a heart rate of 134/min with a blood pressure of 122/94 mm Hg and oxygen saturation of 99%. She had no fever. On auscultation, there were normal bowel sounds. The upper abdomen was diffusely tender to palpation with no abdominal voluntary guarding. Further physical examination of the heart and lungs was completely normal, and there was no lymphadenopathy.

Initial laboratory tests showed only a slightly raised C reactive protein of 14 mg/L (<10 mg/L) with a mild leucocytosis of $16.3 \times 10^9/L$ (4.3 – $10.0 \times 10^9/L$). Other blood counts showed no abnormalities (haemoglobin 169.2 g/L, platelets $247 \times 10^9/L$). CT scan of the abdomen revealed an abnormal aspect of the ileum with thickening of the intestinal wall with surrounding ascites (shown in [figure 1](#)). She was admitted to the gastroenterology department where the abdominal pain spontaneously resolved completely within 2 days. Stool cultures including *Yersinia* remained negative and a workup ultrasound 2 days after admission showed an evident decline of free peritoneal fluid, which was too little to aspirate.

Six and 8 weeks after the first presentation, she experienced two comparable episodes with recurrent acute abdominal pain with transient ascites, which spontaneously resolved within 2–3 days. No provocative factors could be identified in any of the episodes.



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To cite: Hanevelt J, de Vos tot Nederveen Cappel WH. *BMJ Case Rep* 2022;**15**:e250710. doi:10.1136/bcr-2022-250710

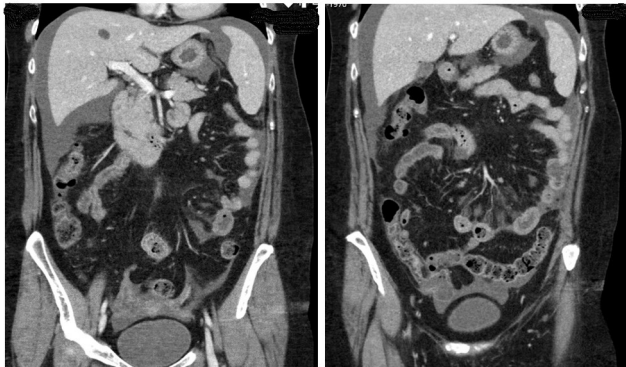


Figure 1 CT scan of the abdomen at initial presentation with thickening of the intestinal wall of the ileum and free peritoneal fluid.

INVESTIGATIONS

Additional research during the second and third admission, including magnetic resonance enterography, ileocolonoscopy and endoscopic ultrasound, showed no abnormalities. Upper gastrointestinal endoscopy performed 5 days after resolution of symptoms revealed a mild antral gastritis. Histology showed no dysplasia, inflammation or *Helicobacter pylori* infection. Repeated abdominal CT displayed increased enlargement of the spleen from 140 mm to 147 mm within 1 month. Supplementary ultrasound showed no portal vein thrombosis, cirrhosis or other findings to indicate portal hypertension as a potential cause of the splenomegaly.

In the third episode, ascites were aspirated. The serum ascites albumin gradient was 13. Ascitic fluid culture including tuberculosis remained negative and cytological examination showed no signs of malignancy. Porphyria was excluded by measuring the level of porphyrins and precursors in urine. Specific additional laboratory tests, performed during the third episode, showed a decreased C1-INH activity of 0.35 E/mL (normal: 0.63–1.82 E/mL) with undetectable low C1q and C4 levels. These results fitted the diagnosis of an acquired C1 esterase inhibitor deficiency.

DIFFERENTIAL DIAGNOSIS

Regarding the clinical picture with colicky abdominal pain, there was initially a high suspicion of symptomatic gallstone disease. However, normal liver biochemistry and external ultrasound, without cholecystolithiasis, made this less likely. Additional endoscopic ultrasound ruled out this diagnosis. Since imaging showed intermittent wall thickening of the small intestine, we considered intussusception as explanation for the transient abdominal pain. As magnetic resonance enterography showed no polyps, tumours or other intraluminal pathology, this diagnosis was also considered unlikely. All findings (abdominal pain, wall thickening of the bowel, ascites and splenomegaly) were difficult to bring under a common denominator. Additional investigations of the ascites unfortunately gave no new insights. Therefore, we expanded our differential diagnosis with more rare and sporadic diseases such as porphyria, mastocytosis and C1-INH deficiency. After observing three episodes, we were able to diagnose an acquired C1-INH deficiency. In the search for an underlying disease taking the splenomegaly into account, a positron emission tomography scan and bone marrow biopsy were performed. The combined findings were suggestive for an SMZL.

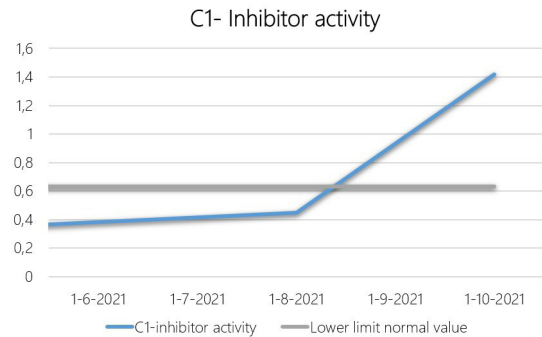


Figure 2 Recovery of C1-inhibitor activity after treatment with four cycles of rituximab.

TREATMENT

In this case, the C1-INH deficiency developed secondary to SMZL. It is usually sufficient to treat the underlying disease, which will also resolve the C1-INH deficiency and its symptoms. SMZL is often an indolent low-grade lymphoma which would not necessarily need treatment in case of asymptomatic patients.⁷ Since our patient experienced disabling symptoms mostly due to the acquired C1-INH deficiency, she was treated with a total of four weekly doses of rituximab monotherapy, which is currently identified as the most effective therapy for SMZL.^{7,8}

OUTCOME AND FOLLOW-UP

To date, she is symptom free for 9 months in which an adequate radiological (normalisation spleen size) and biochemical response (shown in figure 2) were observed. After treatment, she was able to resume her daily activities again.

DISCUSSION

Here, we presented a patient with acute abdominal pain as the first symptom of SMZL, due to an acquired C1-INH deficiency. In this case, the acquired C1-INH deficiency, also named as AAE, displayed itself only with isolated gastrointestinal symptoms without other affected tissues. AAE attacks most frequently affect the face and oropharyngolaryngeal mucosa, and isolated

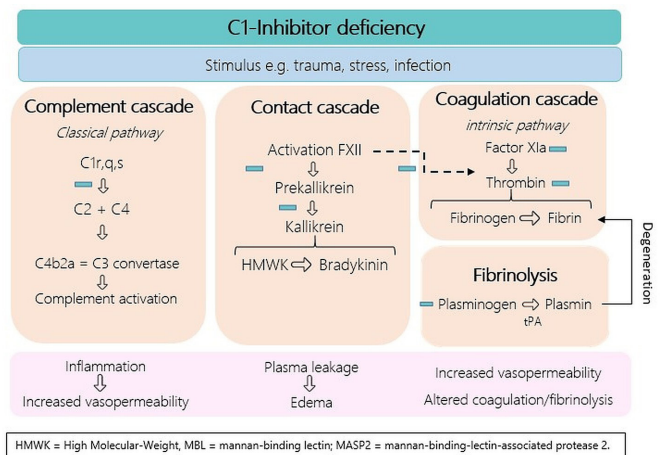


Figure 3 Points of action of C1-inhibitor in complement, contact, fibrinolytic and intrinsic coagulation cascade indicated with the blue minus symbols. In case of a C1-inhibitor deficiency, an excessive amount of bradykinin will be generated, without the need for any provoking stimuli (JH, also based on Morgan¹⁶). HMWK, high-molecular-weight kininogen; tPA, tissue plasminogen activator.

gastrointestinal symptoms are uncommon, which makes the diagnosis in these specific cases challenging.³ The mean frequency of AAE attacks is two times per month with a diagnostic delay that varies from 2 to 5 years.^{3 9 10}

Gastrointestinal manifestations of angioedema may mimic an acute abdomen, and subsequently one-third of these patients undergo unnecessary surgery prior to a definite diagnosis.¹¹ In the present case, there was an interval of 2 months between symptom onset and diagnosis. In this time frame, the patient experienced three attacks of gastrointestinal angioedema which resolved spontaneously within 2–3 days.

The main classification of a C1-INH deficiency is based on its origin and can be roughly divided into two conditions with matching presentations in clinical practice: hereditary and acquired angioedema.¹²

Hereditary angioedema

In case of hereditary angioedema, there is quantitatively too few C1-INH (type 1) or the plasma levels are normal or even elevated, but its activity is insufficient (type 2).¹¹ Both appearances of hereditary angioedema (deficiency or dysfunction of C1-INH) are due to various mutations affecting the SERPING1 gene.^{4 12} In 25% of the cases, the condition arises from a de novo mutation, meaning that a negative family history certainly does not rule out hereditary angioedema.¹³

AAE and associations

AAE presents often secondary to an underlying disease, of which lymphoproliferative disorders are by far most frequently reported.³ These lymphoproliferative disorders are often relatively indolent low-grade lymphomas, with SMZL as the frequent subtype.⁹ The exact pathophysiological mechanisms responsible for the development of AAE are not entirely clarified, but evidence indicates that the C1-INH deficiency can be caused by either C1-INH autoantibodies or excessive consumption of C1-INH by neoplastic tissue.² Autoantibodies are present in a subset of patients with AAE (63%–68%^{3 9}), independent from any underlying disease. Shi *et al* and Zanichelli *et al* showed that patients with AAE secondary to a lymphoproliferative disease were also positive for autoantibodies to C1-INH in 32%–58% of the cases, respectively.^{3 9} Autoantibodies in the present case were not tested routinely and are therefore unknown. Other associated diseases with AAE are monoclonal gammopathy, autoimmune disorders or other solid malignancies.³ Infection with *H. pylori* could potentially also trigger AAE (n=2).^{14 15} In these cases, eradication of *H. pylori* was followed by resolution of symptoms and normalisation of laboratory findings. The main idea here is that presence of *H. pylori* initiates an autoimmune response in which autoantibodies against C1-INH are produced, resulting in increased consumption of C1-INH.

Pathophysiology

C1-INH is a serine protease that regulates and plays an important role in the complement, contact, fibrinolytic and intrinsic coagulation cascade (figure 3–JH, also based on Morgan¹⁶). All these systems are generally activated in case of stimuli, like trauma, stress or infection. In the classic pathway of the complement cascade, C1-INH normally restrains activation of the C1qrs complexes and thereby production of C3 convertase.¹⁷ C1-INH also controls bradykinin released by inhibiting the activation of FXII and prekallikrein in the contact cascade. Bradykinin binds to beta-2 receptors on endothelial cells which subsequently initiates vasodilation and increases vascular permeability.² In case

Patient's perspective

It all started when I did not feel well at one evening during my work. I experienced vague abdominal pain, that suddenly disappeared after only one day. As these complains played up more frequently, I went to the general practitioner to check my blood values. As these results were good, I was referred to the gynecologist for further examinations. An ultrasound showed a polyp in my uterus which was removed. However, the abdominal pain returned. At the start of an attack the abdominal pain was localized in my upper abdomen, progressing over a few hours into my whole abdomen. Besides the pain, I also felt nauseous, sweaty, dizzy and I experienced shortness of breath. I repeatedly contacted my general practitioner and the gastroenterology outpatient clinic, who undertook no direct actions. Unfortunately, the attacks almost always happened in the weekends which made some specific examinations harder to perform. Several hospital admissions followed in a quite short period of time. They took good care of me, and I tolerated all the examinations well. I can't share any negative experience or frustrations about this period, that took quite long. I had moments that I felt sad; however my family had a harder time than me. Happily, I did not experience any attacks since the treatment with the Rituximab. However, shortly after the treatment I felt quite insecure. I was scared to get another attack and afraid that it would affect my throat, as I read that such was possible. Also, COVID affected this period, I had to delay my vaccinations and consequently had to be more at home. Currently, my energy level is a lot less and I am more tired than before the start of this illness. Also, it is very annoying that my working contract is not elongated due to my health situation. Besides this, I returned to my normal daily life, however I still don't feel confident to travel abroad again.

Learning points

- ▶ Acquired angioedema is a very rare cause of acute abdominal pain and should be considered in case of intestinal wall thickening and/or free peritoneal fluid on imaging.
- ▶ Isolated gastrointestinal angioedema is uncommon. Unfamiliarity with this condition among gastroenterologists often leads to a diagnostic delay.
- ▶ Gastrointestinal manifestations of angioedema may mimic an acute abdomen and subsequent, unnecessary surgery prior to definite diagnosis.

of a C1-INH deficiency, whether there is quantitatively too few C1-INH or it is not functioning properly, the inhibitory effect of C1-INH in these systems lacks efficiency. This leads to excessive generation of bradykinin, resulting in local extravasation of fluid and angioedema,¹⁸ as shown in figure 3. In addition, deficiency of C1-INH also causes overactivation of the classic pathway and complement consumption, resulting in undetectable low C1q and C4 levels. In the condition of a C1-INH deficiency, specific stimuli that physiologically are required to activate the complement or contact cascade do not have to be present preceding an attack.¹⁷ Likewise, there were no provoking events preceding the attacks in our described case.

Contributors JH—corresponding author, writing the original draft and visualisation. WHdVtNC—supervision, review and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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