Perioperative Management of a Patient with Hereditary Angioedema and Intestinal Obstruction Secondary to an Ileal Tumor: A Case Report

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Summary
Hereditary angioedema (HAE) is a rare genetic disorder resulting from deficiency or dysfunction of the C1-esterase inhibitor (C1-INH, C1-inhibitor) protein. It manifests with recurrent cutaneous and submucosal edema involving the extremities, abdomen, and/or larynx. Abdominal edema mimics other acute abdominal conditions including intestinal obstruction, potentially prompting unnecessary surgery if misdiagnosed. Prompt treatment with C1-INH typically alleviates abdominal angioedema symptoms within 24 hours, while untreated cases resolve within 2–5 days. Persistence of abdominal symptoms warrants further evaluation for other etiologies of acute abdomen. Surgical procedures with tracheal intubation can induce life-threatening upper airway edema in HAE patients. We describe the successful management of a 41-year-old female with HAE presenting with features of intestinal obstruction, which only partially resolved with the administration of C1-INH and conservative bowel decompressive management. Imaging revealed a small bowel tumor necessitating surgical intervention. Pre-operative prophylactic C1-INH was administered, followed by open laparotomy under general anesthesia with endotracheal intubation. Although C1-INH concentrates are the principal treatment for abdominal HAE attacks, other causes of acute abdomen should be considered, particularly in cases of persistent symptoms, to guide appropriate management. This case highlights the importance of multidisciplinary collaboration and careful perioperative planning to optimize outcomes for HAE patients requiring surgery.

Keywords: Hereditary angioedema, Small intestine, Intestinal obstruction, General surgery, Case report

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Introduction

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent non-pruritic and non-pitting painful cutaneous and submucosal swelling of the face, limbs, and the gastrointestinal and upper respiratory

tracts (1). Its estimated global prevalence in the general population ranges from 1:50,000 to 1:100,000 individuals, affecting all races and genders equally (1-3). The symptoms often overlap with other more common allergic and gastrointestinal conditions, leading to misdiagnosis when there is low clinical suspicion due to low physician awareness (4). Acute HAE attacks are unpredictable, most commonly triggered by physical trauma, including surgery and dental procedures, emotional stress or anxiety, mechanical compression, infection, endogenous and exogenous estrogens, and medications such as angiotensin-converting enzyme inhibitors (1).

Gastrointestinal attacks occur in 25–80% of patients (2), manifesting with moderate to severe abdominal pain, nausea, and vomiting, due to partial or total intestinal obstruction caused by intestinal wall edema. These symptoms mimic other acute abdominal conditions, leading to misdiagnosis and unnecessary surgery (2). Untreated abdominal attacks typically last 2–5 days. Persistent symptoms with fever, peritoneal signs, or leukocytosis should raise suspicion for other acute abdominal pathologies. Surgical interventions pose a risk of swelling at both the surgical and unrelated sites, with the incidence of perioperative angioedema ranging from 5.7% to 30.5% in HAE patients without prophylaxis (5). Besides trauma from the surgical procedure, other factors that influence this risk include anesthesia, psychological stress related to the procedure, underlying disease, and use of compression. Laryngeal edema results from direct mechanical irritation to the mucosa during endotracheal intubation for general anesthesia (6). While no specific epidemiological studies have evaluated the incidence of upper airway obstruction due to endotracheal intubation, Bork et al. found five instances of laryngeal edema arising in three patients within 24 hours post-intubation, among 123 HAE patients who developed sudden upper airway obstruction (7). Laryngeal swelling manifests with stridor, respiratory distress, laryngospasm, and bronchospasm, and can progress rapidly from mild discomfort to complete airway obstruction. It is a life-threatening emergency due to the risk of asphyxia, with a mortality rate of 15–33% if untreated (6, 8).

We present a case of a patient with HAE who presented with acute abdomen and was successfully managed under general anesthesia with endotracheal intubation during abdominal surgery. The goal of this report is to increase awareness of HAE, to highlight the available treatment options, and to describe the perioperative management.

Case presentation

A 41-year-old female known to have HAE was referred to our tertiary level teaching and referral hospital with acute abdomen due to small bowel obstruction. Her regular medications included a prophylactic plasma-derived C1-inhibitor (pdC1-INH) concentrate (Cinryze®, Takeda, Japan) and/or Icatibant (Firazyr®, Takeda, Japan), a bradykinin receptor antagonist, having previously been on long-term danazol. Her family history included HAE on the paternal side. She had a 4-day history of abdominal pain, vomiting, and constipation. Examination revealed a sick-looking, normotensive, and afebrile patient with a distended, tender abdomen but no palpable organomegaly or extremity edema. Other organ systems were unremarkable. Laboratory investigations showed a mild neutrophilia of $11.17 \times 10^3/\mu l$ and mildly elevated C-reactive protein (CRP) of 56.9 mg/L, with normal liver function, urea, and electrolytes.

Abdominal angioedema was suspected, and she was infused with 1000 international units (IU) of C1-INH concentrate and intravenous (IV) fluids and maintained on nil per oral (NPO) intake. Abdominal pain alleviated within 24 hours, and she started passing flatus. Oral sips and self-ambulation were initiated, and the abdominal distension resolved on the third day of admission. She transitioned to a light diet on day 4, but subsequently developed bloating, abdominal pain, and bilious post-prandial vomiting. She was reverted to NPO, with total parenteral nutrition and gastric decompression via a nasogastric tube. Maintenance IV fluids continued, and 1000 IU of C1-INH was infused then and every third day thereafter. There was pain relief and passage of flatus, but the vomiting recurred, two to three times a day upon re-introduction of oral sips. The persistent vomiting necessitated further evaluation, but the patient was

unable to retain oral contrast. An abdominal radiograph was thus done on day 6 to assess for overt intestinal obstruction, revealing distended loops of bowel. The vomiting resolved by day 12, permitting a contrast-enhanced computed tomography (CT) of the abdomen and pelvis, which showed a partially delineated enhancing proximal ileal mass with intraluminal extension, luminal narrowing, and dilatation of the proximal small bowel. There was an associated contiguous spiculated mesenteric mass, perilesional adenopathy, mild concentric wall thickening of the colon, suggestive of intestinal angioedema, and poorly delineated enhancing lesions in the liver (Figure 1).

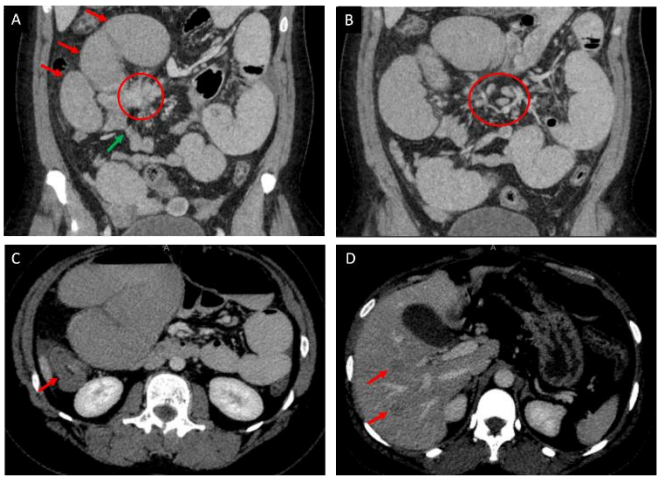

Figure 1.
A. Coronal CT image of the abdomen and pelvis showing an ileal tumour (red circle), proximal distended loops of bowel (red arrows) and distal luminal narrowing (green arrow). B. Coronal CT image of the abdomen and pelvis showing perilesional adenopathy (red circle). C. Axial CT image showing circumferential thickening and oedema of the colon (red arrow). D. Axial CT image showing liver lesions (red arrows)

A diagnosis was made of a small bowel ileal mass with mesenteric metastasis (differential diagnosis of carcinoid tumor), and associated small bowel intestinal obstruction, requiring surgery. After multidisciplinary discussion, the patient and her next of kin were fully appraised of the immunological, anesthetic, and surgical risks, and they gave written informed consent for laparotomy, tumor resection, and bowel anastomosis. Pre-operatively, the patient received 2000 IU of C1-INH, with two additional doses and 6 units of fresh frozen plasma (FFP) kept ready in the event of post-operative angioedema. General anesthesia was induced with fentanyl 150 µg, propofol 150 mg, and rocuronium 80 mg, and rapid sequence intubation performed smoothly with a 6.5-mm endotracheal tube which was cuffed at 20 cm.

Intra-operatively, an ileal tumor was found 120 cm from the ileocecal junction, causing intestinal obstruction with proximal dilatation and distal collapse. The bowel was decompressed and the ileal segment with tumor resected. Side-to-side ileo-ileal anastomosis was performed. Post-surgery, the patient was reversed successfully, spontaneous breathing restored, and extubated with minimal stimulation. Her vital signs were stable, and she was admitted in the high-dependency unit for 48 hours to monitor for late-onset airway edema. The post-operative period was uneventful, and she was discharged after 6 days. She visited the outpatient clinic 2 weeks after discharge and reported no significant event. Histopathology confirmed a well-differentiated small cell neuroendocrine carcinoma prompting referral to an oncologist for further management.

Discussion

This is the first documented report of surgical intervention in a patient with HAE in our setting. HAE is a rare, autosomal dominant genetic disease characterized by recurrent episodes of severe swelling. There are three types of HAE, distinguished by the underlying cause and levels of the C1-INH protein. Types I and II are caused by mutations of the *SERPING1* gene, resulting in deficient (type I) or dysfunctional (type II) C1-INH. Type I comprises 80–85% of cases while type II accounts for 15–20%. Type III, the rarest form, is caused by a mutation in the *F12* gene which codes for coagulation factor XII (FXII). It is associated with normal C1-INH level (1). C1-INH regulates the complement, coagulation, fibrinolytic, and contact activation/kinin pathways. In the kinin pathway, C1-INH inactivates plasma kallikrein, controlling the production of bradykinin. Deficiency or dysfunction of C1-INH leads to uncontrolled release and activity of bradykinin, causing vasodilatation, increased vascular

permeability, and subcutaneous and mucosal edema (1). FXII is involved in bradykinin production, and the mechanism of swelling in type III HAE is thought to involve enhanced bradykinin signaling (1). All types of HAE are symptomatically indistinguishable, manifesting with recurrent episodic skin, abdominal, and upper airway swelling. The diagnosis should be considered in patient presenting with recurrent cutaneous, non-pruritic, non-pitting angioedema without urticaria, and/or recurrent, unexplained severe abdominal pain and swelling (1). Confirmation of the diagnosis requires laboratory measurement of complement C4 protein level and C1-INH antigenic and functional levels. A decreased C4 level (<30%) during an attack prompts further testing with C1-INH antigenic and functional assays, while a normal C4 level during an attack supports considering alternative diagnoses (1).

Management of HAE involves treating acute attacks, short-term prophylaxis, and long-term prophylaxis. The recommended on-demand treatment for acute attacks is a pdC1-INH to replace the missing or dysfunctional C1-INH, or ecallantide (a kallikrein inhibitor), or icatibant (a bradykinin receptor antagonist) (9). Most patients experience relief within 2 hours of administration of these agents, but a major swelling may take up to 24 hours to resolve completely. Response is quicker when treatment is initiated early in the course of the attack. In our case, the C1-INH was initiated late, 4 days from initial presentation. If these drugs are unavailable, FFP can be used, as it contains C1-INH (9). Unlike allergic or idiopathic angioedema, HAE attacks are not mediated by histamine and do not respond to antihistamines or corticosteroids.

Short-term prophylaxis with a pdC1-INH is mandatory before any dental, medical, or surgical procedures; it has a long half-life and provides the missing or dysfunctional protein up to 1 or 2 days after the procedure. The prophylaxis should be administered as close as possible to the start of the procedure (at least an hour), at a dose of 1000 units or 20 units/kg (9). Where a pdC1-INH is not available, FFP can be used for short-term prophylaxis (2 units in adults or 10 mL/kg in children, administered within 1–6 hours before the procedure) (8, 10). The attenuated androgen danazol may also be used for short-term prophylaxis (6–10 mg/kg/day in three divided doses), 5 days before and 2 days after the procedure (9). Danazol works by increasing hepatic synthesis of C1-INH (11). Long-term prophylaxis with either a pdC1-INH (first-line treatment) or danazol (second-line treatment) is beneficial for patients who experience frequent and/or severe episodes (9). Despite prophylaxis, acute attacks may still occur, and danazol is ineffective in treating them. Also, significant side effects of androgens have been documented (9, 11).

Abdominal angioedema is a frequent manifestation of HAE characterized by moderate to severe abdominal pain, vomiting, and/or diarrhea. It causes intestinal wall swelling that is detectable on CT scan, along with ascites, and in rare cases, hypovolemic shock. The swelling worsens within 12–36 hours, reaching its peak intensity before gradually resolving over 2–5 days. The clinical presentation and imaging findings mimic other causes of acute abdomen, potentially precipitating unnecessary surgery if misdiagnosed (12). Hahn et al. reported that HAE patients are 2.5 times more likely to undergo abdominal surgery, compared to individuals without HAE (13). Awareness of angioedema pathology in patients presenting with recurrent abdominal symptoms is important for accurate diagnosis and appropriate treatment. Detailed patient and family histories, careful physical examination, imaging, and knowledge of types of angioedema are key for correct diagnosis and management (12). Documented history of HAE in our case informed initial management with C1-INH concentrate. Not every abdominal symptom in HAE patients, however, is attributable to angioedema, as they can also suffer from other acute abdominal conditions. While C1-INH administration may initially alleviate symptoms, recurring issues require further evaluation, considering potential concomitant gastrointestinal disorders, as illustrated in our case.

Surgical trauma and perioperative anxiety can trigger acute HAE exacerbations, provoking episodes of swelling in the extremities, abdomen, and/or upper airway, regardless of the site of surgery (9, 14). Lack of awareness about HAE increases the likelihood of complications and mortality in these patients, as they

will not be treated correctly (4). Patients should be informed in detail about the risks and possible complications of the procedure. Perioperative anxiety should be well managed as it can cause emotional stress, an important trigger for HAE attacks. A survey of patients living with HAE in the United States reported that at least 85% of respondents live in constant fear of sudden airway closure due to laryngeal swelling from dental, medical, and surgical procedures (15).

An appropriate perioperative management plan with multispecialty collaboration involving surgeons, anesthesiologists, critical care physicians, hematologists, and allergy/immunology practitioners is paramount before any surgical procedure, to minimize the likelihood of post-operative HAE attacks and premature mortality. There are currently no universal guidelines for managing HAE patients in the perioperative setting. Recommendations, however, include short-term prophylaxis before procedures, identification of triggers for acute attacks, minimizing airway manipulation, and avoiding intubation if possible (8, 9). Minimally invasive surgery under local or regional anesthesia, or sedation is preferred, to minimize the risk of trauma. Not every patient, however, is a candidate for these approaches, making prophylactic replacement of the missing/dysfunctional protein crucial for perioperative management, as illustrated in this case. Our patient required a high abdominal incision and had a full stomach, and thus was at risk for aspiration. Pre-procedural prophylaxis does not guarantee that attacks will not develop post-procedure angioedema, so patients must be kept under surveillance post-operatively and rescue medication (C1-INH or FFP) should be readily available for treatment of breakthrough attacks (9). To prevent post-operative laryngeal edema, an endotracheal tube of adequate size should be used, the duration of intubation should be minimized, and cuff pressures should be measured regularly to prevent tracheal stimulation due to high cuff pressure (16). HAE patients should be carefully monitored for at least 36 hours post-operatively for indicators of airway edema such as labial edema, hoarseness of voice, stridor, and dyspnea (6).

Conclusion

Awareness of HAE is key for appropriate care. Gastrointestinal attacks though mimicking surgical emergencies should be managed medically with C1-INH concentrates. Persistent or unresolving symptoms necessitate further evaluation and may require surgical intervention. Successful perioperative management involves multidisciplinary collaboration, appropriate prophylaxis, and vigilant patient monitoring.

Informed Consent

The patient provided written informed consent for the medical interventions and publication of anonymized case details presented in this report. Ethical approval for publication was granted by the institutional review board (KNH-ERC/01/PUB/2).

Author contributions

APG, AKB and IKM equally contributed in conceptualization. APG and AKB equally contributed in writing of the original draft. IKM, SN, DK and EOW equally contributed in reviewing & editing of the original draft.

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