

# C-prime esterase inhibitor deficiency presenting as intestinal pseudo-obstruction and angioedema

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**ABSTRACT:** A 17-year-old man presented with episodic abdominal pain, distension and vomiting. Esophageal manometry showed a reduced lower esophageal pressure with massive reflux, gastric emptying of liquids was normal and migrating myoelectric complexes were present on small bowel motility tracing. Full thickness surgical biopsies from the upper jejunum, mid-small bowel and ileum showed a normal villus pattern but a reduction in the number of neurons in the myenteric plexus, degeneration and shrinkage of some of the persisting neurons in the myenteric plexus and swelling of the accompanying nerve fibres and Schwann cells. This was interpreted to be compatible with intestinal neurogenic pseudo-obstruction. He initially responded to glucocorticosteroids with reduction in the frequency and severity of these symptoms, accompanied by weight gain and a 14 cm growth in height. The steroids were stopped after two years, but within weeks his pain and distension returned. He then developed symptoms of angioedema, with markedly reduced C<sup>1</sup> esterase inhibitor activity and reduced C<sub>4</sub>. Both the symptoms of angioedema and pseudo-obstruction were well controlled with stanazolol. His younger brother later developed similar symptoms, also had C<sup>1</sup> esterase inhibitor deficiency, and also responded to stanazolol; an older brother had previously had similar symptoms which were lost over time. This suggests that C<sup>1</sup> esterase inhibitor deficiency may produce symptoms indicative of intestinal obstruction. *Can J Gastroenterol* 1988;2(2):60-64

**Key Words:** Angioedema, C<sup>1</sup> esterase inhibitor deficiency, Pseudo-obstruction

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C-PRIME ESTERASE INHIBITOR DEFICIENCY is the most common genetically inherited disorder of complement inhibition, producing a syndrome of recurrent angioedema characterized by swelling of face, larynx, bowel wall, genitalia and extremities. The inheritance is of autosomal dominant mode, although a rarer acquired form may occur. In one study of 104 cases, attacks of swelling affected the subcutaneous tissue, the upper airway and the bowel mucosa in 86%, 76% and 75% of patients, respectively (1). More than half of the patients had onset of the symptoms of the disease before 12 years of age; 12 to 18% of patients underwent unnecessary surgery because of an erroneous diagnosis (1,2).

About three-quarters of patients may present with symptoms of abdominal pain or vomiting (1-4). The diagnosis may be obscured by the absence of cutaneous, oropharyngeal and respiratory involvement (5). Abdominal films may show evidence of thumb-printing and mucosal edema (2,3). Respiratory obstruction due to laryngeal edema can

be fatal without appropriate treatment. Prodromes of attacks are described by one-half of the patients as a feeling of 'discomfort' or anxiety, starting 24 h before the attack (1,2). Also, one-half of the patients can identify triggering factors such as foods, local trauma (ie, dental procedures), anxiety and psychological stress (1,2).

The biochemical defect is deficiency of C<sup>1</sup> esterase inhibitor or production of an inactive inhibitor. This will cause uncontrolled activation of the complement system; activation of the plasma kallikrein system leads to formation of vasoactive substances (6). The diagnosis can be confirmed by the reduced level of C<sup>1</sup> esterase inhibitor or the presence of functional inactive inhibitor. C<sub>2</sub> and C<sub>4</sub> are both reduced during acute attacks.

Antihistamines, corticosteroids and adrenaline are usually not effective for the treatment of hereditary angioedema. Treatment of acute attacks would include infusion of C<sup>1</sup> esterase inhibitor concentrate or fresh, frozen plasma which contains the inhibitor (1,7,8). There is a theoretical danger that fresh frozen plasma may supply substrate for C<sup>1</sup> and therefore perpetuate the attack. Antifibrinolytic agents such as aminocaproic acid or transexamic acid are potent inhibitors of plasma which may activate C<sup>1</sup> and can be used in preventative therapy. These agents can, however, cause serious adverse effects (8,9); both can induce rhabdomyolysis and thrombosis. In addition, transexamic acid has tumourigenic potential.

Androgen derivatives such as oxymetholone, stanozolol and danazol are effective in preventing attacks of angioedema (8-10). The potential adverse effects include masculinization and menstrual disorders in women, diminished spermatogenesis in men, peliosis hepatitis, benign hepatomas and hepatic carcinoma. Androgen derivatives should be avoided in pregnant women or children. Patients with infrequent or mild attacks of hereditary angioedema may not need to be treated with drugs. Before dental procedures, these patients should receive either C<sup>1</sup> esterase inhibitor concentrate or a short course of androgen derivatives.

## CASE PRESENTATION

The case of a young man with symp-

toms and pathological changes compatible with familial neurogenic pseudo-obstruction, associated with C<sup>1</sup> esterase inhibitor deficiency is described.

The patient was a caucasian male who was 17 years old when he was initially referred to the Gastroenterology Teaching Clinic, University of Alberta in 1980 for investigation of episodic abdominal pain and vomiting, thought to be due to irritable bowel syndrome.

Because of crampy periumbilical abdominal pain associated with vomiting, he had had a laparotomy in 1974 for suspected appendicitis. The appendix was normal but the terminal ileum was noted to be questionably inflamed. He subsequently had several upper gastrointestinal series with follow-through examinations, which demonstrated a possibly abnormal terminal ileum, but no definitive diagnosis was made.

A duodenal ulcer was suspected on barium meal examinations performed in 1975 and 1977. He had no pain to suggest active peptic disease and the radiological abnormalities were not treated. He had intermittent abdominal pain and vomiting. The pain was described as severe dull epigastric discomfort, associated with distension, burping and flatulence. He developed vomiting of partially digested food anywhere from 12 to 36 h after the onset of the pain. Once the episodes of vomiting stopped, his abdominal pain improved. The frequency of these attacks varied from once every four weeks, to once weekly. There was no history of diarrhea or dysphagia.

The physical examination in 1980 was unremarkable, apart from the presence of a prominent gastric succussion splash which was audible 3 h after ingestion of a small meal. There were no features of scleroderma, palpable thyroid or neurological abnormalities, including no clinical evidence of autonomic dysfunction.

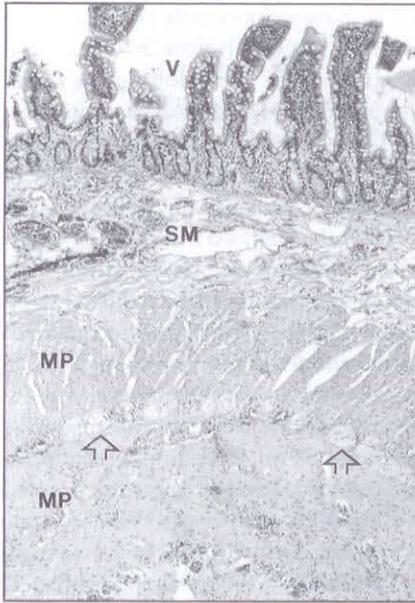
A gastroscopy in 1980 revealed a dilated stomach and the ACMI panendoscope could be introduced 1 to 2 cm past the pylorus. There was no evidence of ulcer in either the stomach or the duodenum. Small bowel enteroclysis showed mucosal thickening of the descending duodenum. A small bowel mucosal biopsy was subsequently found to be unremarkable. He was initially treat-

ed with metoclopramide (Maxeran; Nordic) 10 mg qid before meals and at bedtime. The metoclopramide made him nauseated and it was discontinued.

The patient continued to experience the symptoms of pain, vomiting, distension and excess gas, therefore, he was further investigated in 1981. The upper gastrointestinal and follow-through examination demonstrated a dilated stomach with thickening of the mucosal folds of the duodenum and jejunum. The barium enema was unremarkable, with reflux of barium into a normal appearing terminal ileum. A technetium-sulphur colloid gastric emptying scan performed when the patient was symptomatic showed a normal gastric half-emptying time for liquids of 92 mins. Esophageal motility study (including a pH probe) showed massive gastroesophageal reflux, but the motility of the body of the esophagus was normal.

Because of the concern that the abnormal radiological appearance of the small intestine represented lymphomatous infiltration, exploratory laparotomy was performed. There was approximately 700 mL of clear fluid within the peritoneal cavity and this fluid was sent for culture and cytology, which were negative. The entire upper half to two-thirds of small bowel was thickened and edematous. Sections of full thickness surgical biopsies (Figures 1 and 2) from the upper jejunum, mid-small bowel and ileum showed: swollen myenteric plexus at all levels of small bowel examined (ie, upper jejunum, mid- and small intestine and ileum); moderate submucosal edema from the upper jejunum and mid-small intestine, but not from the ileum; intestinal villi well preserved at all levels; swollen ganglia in the myenteric plexus at all levels, an apparent reduction in the number of neurons and enlargement and fine vacuolation of Schwann cells (also present were dark, shrunken neurons with misshapen perikarya and irregular processes, and neurons with swollen perikarya and intra-nuclear vacuoles); Schwann cells were not increased in numbers (Schwannosis); identical but much less severe changes were observed in ganglia of the submucous nerve plexus.

Because of the failure of the metoclopramide, the severity of symptoms and the minimal congestion and edema in the



**Figure 1)** Survey photomicrograph of full thickness biopsy of the ileum, showing swelling of the myenteric plexus (open arrow), located between the inner circular and the outer longitudinal layers of the muscularis propria (mp). The submucosa (sm) is free from edema at this level. Intestinal villi (v) are well preserved. (Hematoxylin and eosin,  $\times 42$ )

submucosa, the patient was started on prednisone 20 mg daily. He quickly did well, with no further attacks of abdominal pain and vomiting for about two years. He grew 14 cm and gained 22.7 kg. The prednisone was then gradually

stopped and a repeat upper gastrointestinal series with follow-through examination was entirely normal.

Several months later while off prednisone, the patient developed nausea, vomiting and, a new symptom, constipation. He was readmitted while off prednisone and while having symptoms. Small bowel motility studies demonstrated an abnormal tracing, but migrating myoelectric complexes were present. Cisapride 10 mg bid was started and this was followed by improvement in his constipation, but the nausea and vomiting persisted.

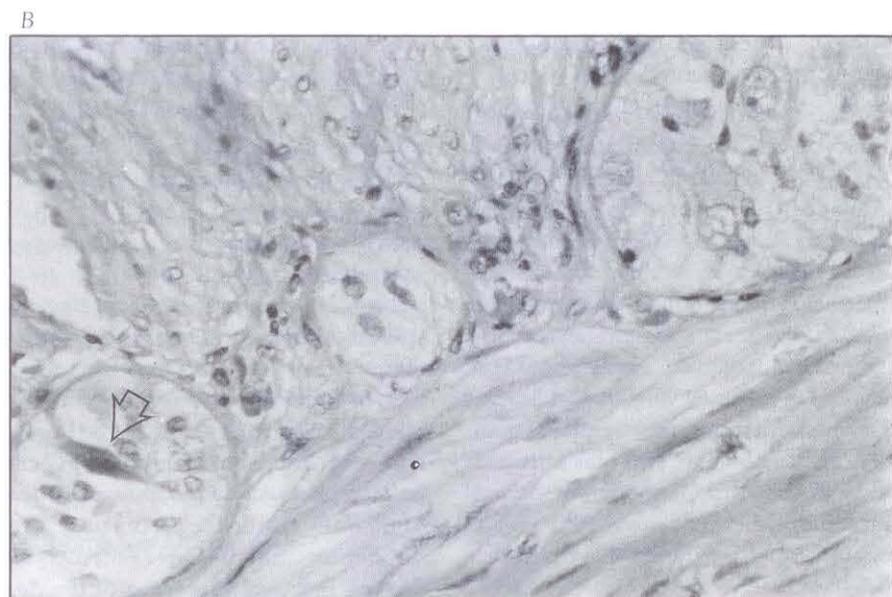
In September 1984, episodic swelling of the lips, throat and hands developed. These episodes of swelling were associated in time with nausea, abdominal pain and vomiting. C<sup>1</sup> esterase inhibitor activity was nonreactive and there was a markedly reduced C<sub>4</sub> of 0.02 (normal, 0.2 to 0.4). These laboratory abnormalities are consistent with the diagnosis of angioedema. He was treated with stanazolol, 4 mg a day and quickly became asymptomatic, with no recurrence of swelling, abdominal distress or nausea and vomiting over a follow-up interval of two years.

The patient's younger brother also developed episodes of swelling of the hands, episodes of pain, nausea and vomiting. He also had reduced C<sup>1</sup> ester-

ase inhibitor and responded to stanazolol. An older brother had similar symptoms of pain, nausea and vomiting which remitted spontaneously; his C<sup>1</sup> esterase inhibitor activity is unknown.

## DISCUSSION

Intestinal pseudo-obstruction is a clinical syndrome characterized by acute or chronic symptoms and signs of intestinal obstruction, in the absence of mechanical or obstructing lesions (11,12). Often the entire gastrointestinal tract is involved; for example, esophageal motility is generally abnormal and differs in those patients with disorders of the smooth muscle or the autonomic system (13). It may also be subdivided into a primary (or idiopathic) and a secondary form. Primary chronic intestinal pseudo-obstruction is uncommon. Therefore, it is essential to have a high index of suspicion for some of the secondary causes of pseudo-obstruction, such as diabetes or scleroderma (14-21). Colonic pseudo-obstruction (Ogilvie's syndrome) may occur in surgical patients, especially in those having orthopedic procedures or exposed to blunt trauma, and may be compounded by associated diabetes, uremia, cardiac failure, cancer or narcotic addiction (22,23). The present patient had apparent familial neurogenic intestinal pseudo-obstruction and symptomatic re-



**Figure 2)** Swollen ganglia in the myenteric plexus of the jejunum and ileum, showing an apparent reduction in the number of neurons and enlargement and fine vacuolation of Schwann cells. (A) Dark shrunken neurons with misshapen perikarya and irregular processes (arrows); (B) Neurons with swollen perikarya and intranuclear vacuoles (arrows). (Hematoxylin and eosin A  $\times 215$ , B  $\times 300$ )

lief was initially achieved with prednisone, but the development of angioedema led to the suspicion and demonstration of C<sup>1</sup> esterase deficiency responding to stanazolol.

The known secondary causes of pseudo-obstruction are shown in Table 1, and newer causes are being reported (24). With idiopathic intestinal pseudo-obstruction, abnormalities may be found in either the smooth muscle or myenteric plexus (25-34). Rarely, no histological abnormality of the smooth muscle or myenteric plexus is detected (27,29).

Familial visceral neuropathy and myopathy have been described in some cases of chronic intestinal pseudo-obstruction (11,29-30,32). The transmission may be autosomal dominant, autosomal recessive, or X-linked dominant. Commonly these familial syndromes of intestinal pseudo-obstruction may be associated with both abnormalities of the gastrointestinal and urinary tracts (11,29,34). This patient had two brothers with similar symptoms, one of whom also had proven C<sup>1</sup> esterase inhibitor deficiency.

In patients with pseudo-obstruction, a full thickness intestinal biopsy for examination of smooth muscle and myenteric plexus may be normal or may show muscle hypertrophy, atrophy or replacement with collagen (11,32,35,36). Silver impregnation can be of assistance in examining the myenteric plexus (37). The plexuses may be hypertrophic but more commonly show degeneration. Many of the neuronal abnormalities also can be detected by conventional light microscopy. The abnormalities of intestinal smooth muscle are classified as degenerative changes and/or atrophy. It is essential to use a trichrome stain for collagen because the usual hematoxylin and eosin stain may not be capable of demonstrating a small number of collagen fibres. The biopsy findings in this patient (Figures 1 and 2) are similar to those previously described in the literature.

Management of this syndrome has to be tailored according to the individual patient. The prognosis also varies and may be poor in some patients. Cholinergic drugs and metoclopramide usually fail to improve the symptoms (38-40). Diarrhea related to bacterial overgrowth can usually be controlled by the use of

oral antibiotics such as tetracycline or metronidazole (26). Dietary manipulations are of little value (26). Total parenteral nutrition is useful for treatment of the symptoms and for improvement of the nutritional status (26,27,31,41,42). Use of steroid has been infrequent in the management of this syndrome (31). Glucocorticosteroids were used in this patient because of the albeit modest congestion and edema in the small bowel. In retrospect, these histological changes may have been due in part to the angioneurotic edema which certainly must have been present at that time.

TABLE 1

**Causes of chronic intestinal pseudo-obstruction**

Collagen diseases
Progressive systemic sclerosis
Dermatomyositis polymyositis
Systemic lupus erythematosus
Ehlers-Danlos syndrome
Endocrine disorders
Myxedema
Diabetes mellitus
Pheochromocytoma
Hypoparathyroidism
Neurological disorders
Myotonic dystrophy
Parkinson's disease
Familial autonomic dysfunction
Psychosis
Viral illness
Varicellar-Zoster
Cytomegalovirus
Miscellaneous
Jejunioileal bypass
Jejunal diverticulosis
Amyloidosis
Celiac-sprue
Duchenne's muscular dystrophy
Chagas' disease
Sclerosing mesenteritis
Drugs

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Many patients with pseudo-obstruction, including the present patient, will at least have had an exploratory laparotomy for diagnostic purposes. Various enteric anastomosis or bypass procedures have been described (26,27). Resection of affected bowel, such as colectomy, may be indicated in certain patients (26,28,29,43), although patients often do poorly after surgical procedures and are best treated conservatively.

The exact relationship of angioneu-

rotic edema with this patient's apparent pseudo-obstruction is difficult to establish. This patient had obvious abnormalities of the myenteric plexus in full thickness small bowel biopsies, and these changes presumably represent the basis for the alterations in small intestinal motility which others have noted (14), but these could not be confirmed with testing on a single occasion. Because of the mild edema of the submucosa, glucocorticosteroids were used in the initial management; this was successful for a full two years' duration. Symptoms recurred following the cessation of steroid therapy, confirming their efficacy in management of the condition. Concerned about the long term dangers of the use of steroids, therapy was not restarted once the patient had completed growing. Later, he developed symptoms of angioedema and stanazolol was started; he has since remained asymptomatic over a follow-up interval of over two years.

In summary, this patient had obstructive complaints initially thought to be due to a mild form of idiopathic familial pseudo-obstruction secondary to degenerative changes in the myenteric plexus. The authors hypothesize that he became intermittently symptomatic because of the episodic attacks of angioedema which in addition to involving his face and arms, involved his upper gastrointestinal tract. C<sup>1</sup> esterase inhibitor deficiency may be a treatable contributor to the symptoms of intestinal pseudo-obstruction.

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## Clinical Quiz

Please note, there may be more answers than asked for in the question.

### LIVER

1. A 22-year-old man is referred for assessment of possible Wilson's disease. Name six ways in which this disease may present.
2. A 37-year-old male homosexual is a known hepatitis B carrier. After a two-week holiday in New York he presents to his physician with tiredness and malaise. The physician suspects this is due to his liver condition. What are eight causes for 'flare' of disease activity in a hepatitis B carrier? (Answers page VIII)



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