Reminder of important clinical lesson

Another 'Cushing ulcer'

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Summary

The authors describe the case of a 39-year-old man who presented to our hospital with easy fatigability and malaise. On physical examination, hypertension was noted without any cushingoid appearance. Laboratory testing revealed normochromic-normocytic anaemia with positive results of occult blood in the stool, hyperglycaemia and hypokalemia. Upper endoscopy revealed active gastric ulcer with *Helicobacter pylori* infection, likely causing gastrointestinal bleeding. Endocrine examinations showed that both serum adrenocorticotrophic hormone and cortisol were elevated with loss of diurnal variation. A diagnosis of Cushing's disease secondary to pituitary adenoma was made as results of brain MRI and blood sampling from inferior petrosal sinus. In a patient with peptic ulcer disease, physician should be alert to the possible endocrine background.

BACKGROUND

Peptic ulcer disease (PUD) can be secondary to hormonal abnormalities. Elevated serum gastrin due to gastrinoma¹ or histamine due to systemic mastocytosis,² carcinoid syndrome³ or basophilia associated with haematologic disorders⁴ can cause PUD with acid hypersecretory states.

Cushing's syndrome is an endocrine disease caused by excess secretion of adrenocorticotrophic hormone (ACTH) in 80–85% of cases, usually by a pituitary corticotroph adenoma (Cushing's disease), less often by an extrapituitary tumour (ectopic ACTH syndrome) and very rarely by an ectopic corticotrophin releasing hormone-secreting tumour (ectopic CRH syndrome).⁵ About 15–20% of patients have ACTH-independent Cushing's syndrome.⁵ In adults, persistent excess cortisol production can result in a variety of clinical symptoms such as central obesity, cervical fat pad, thinned skin, purple striae, proximal muscle weakness, fatigue, high blood pressure, glucose intolerance, acne, hirsutism, menstrual irregularity and depression.⁵ However, despite the widespread impression that excess of corticosteroids has ulcerogenic potential, only a few reports describe gastrointestinal (GI) complications in patients with Cushing's syndrome.⁶

We present here an adult case with gastric ulcer associated with Cushing's disease tilted 'Another 'Cushing ulcer', which is distinguished from true Cushing ulcer, a condition with gastric ulcer associated with elevated intracranial pressure. The relationship between excess of corticosteroids and upper GI mucosal damage is discussed.

CASE PRESENTATION

A 39-year-old man admitted to our hospital presenting with 3-month history of easy fatigability, malaise and weight loss of 6 kg. Five days prior to admission, he noticed transient passage of black tarry stool with no epigastric or abdominal pain. He had no medical and familial history of diabetes mellitus, hypertension and GI or endocrine disorders. He had taken no ulcerogenic drugs including aspirin or non-steroidal anti-inflammatory drugs (NSAIDs). He

had been smoking a pack per day for 20 years. He was 176 cm in height and weighted 67 kg. The blood pressure was 148/100 mm Hg, the pulse rate was 60 bpm, and body temperature was 36.2°C. On physical examination, the skin was pale without any cushingoid appearance. A digital rectal examination revealed no masses, fissures and haemorrhoids but positive results of occult blood in the stool. The rest of physical and neurological examination was unremarkable.

INVESTIGATIONS

Laboratory examination showed a white cell count of 8200/μl with a shift to the left, and a haemoglobin of 7.9 g/dl with mean corpuscular volume of 99.3 fl (reference range: 83–105 fl). The serum potassium was 3.2 mEq/l (reference range: 3.5–4.7 mEq/l) with no other electrolyte abnormalities, fasting glucose 294 mg/dl (reference range: 70–109 mg/dl) with haemoglobin A1c of 8.6% (reference range: 4.5–6.2%).

Upper endoscopy revealed active ulcer in the gastric angle, likely causing GI bleeding (figure 1). A rapid urease test was positive for *Helicobacter pylori* infection. Total colonoscopy showed no specific abnormalities potentially causing GI bleeding.

As coexisting hyperglycaemia, hypokalemia and no family history raised a suspicion of having a secondary hypertension, endocrine examinations were performed, showing elevated basal serum ACTH of 115 pg/ml (reference range: 9.0–52.0 pg/ml) and cortisol of 25.5 μg/dl (reference range: 4.0–19.2 μg/dl) with loss of diurnal variation. Basal serum gastrin levels were within normal limits. Both low-dose (1 mg) and high-dose (8 mg) overnight dexamethasone suppression tests showed that neither serum ACTH nor cortisol levels were suppressed. Brain MRI with gadolinium enhancement detected a hypointense pituitary tumour suggestive of a microadenoma (figure 2). The results of inferior petrosal sinus sampling is shown in table 1. On the basis of these investigations, the patient was diagnosed as ACTH-dependent Cushing's syndrome (Cushing's disease).

Figure 1 Upper endoscopy reveals active ulcer in the gastric angle, likely causing GI bleeding.

Table 1 Results of inferior petrosal sinus sampling

Site of blood sampling	Serum ACTH level (pg/ml)
Right inferior petrosal sinus	52 000
Left inferior petrosal sinus	33 200
Periphery	372

TREATMENT

The patient was treated with iron supplementation and *H pylori* eradication therapy. Antihypertensive medications combined with insulin therapy were also initiated.

OUTCOME AND FOLLOW-UP

Successful *H pylori* eradication therapy resulted in ulcer healing. The anaemia normalised with iron supplementation alone. After the control of hypertension and hyperglycaemia, he was transferred to the department of neurosurgery. After he was successfully treated with a transsphenoidal pituitary adenomectomy, his endocrine abnormalities eventually resolved with no further medications and his body weight decreased to 60 kg.

DISCUSSION

The possible ulcerogenic mechanisms of corticosteroids

To date, several theories on mechanism by which corticosteroids might compromise the gastric mucosa have been proposed: decreased gastric mucus secretion⁷; delayed ulcer healing with inhibition of mucosal prostaglandin synthesis⁸; enhancement of gastric cell hyperplasia with augmented acid secretion.⁹

The incidence of PUD in Cushing's syndrome

Despite the widespread impression that excess of corticosteroids has ulcerogenic potential, the true incidence of PUD or GI bleeding in Cushing's syndrome remains to be clarified due to the lack of epidemiological evidence.

Shepherd *et al*⁶ reported that among 23 patients with ectopic ACTH syndrome associated with small-cell lung cancer, six patients had PUD and four had upper GI bleeding. However, in this study, the incidence of PUD may not reflect that in overall Cushing's syndrome cases because many patients enrolled were serious malignancy-related conditions under chemotherapy, which likely to be predisposing factors to the upper GI mucosal damage.

The major risk factors for PUD

The pathogenesis of PUD is considered to be multifactorial. Among the risk factors of PUD, NSAIDs use and *H pylori* infection are major aetiopathogenetic factors and synergistically increase risk for PUD. In a meta-analysis of NSAIDs takers,¹⁰ uncomplicated PUD was more common in patients positive for *H pylori* than in those negative (41.7% vs 25.9%), which give a summary OR of 2.12 (95% CI 1.68 to 2.67). In a meta-analysis of five case controlled studies,¹⁰ in patients with negative *H pylori* infection, NSAIDs use increases the risk of PUD compared to non-NSAIDs use (OR=19.4 (95% CI 3.14 to 120)). In patients with non-NSAIDs use, positive *H pylori* infection increases the risk of PUD compared to negative infection (OR=18.1 (95% CI 2.64 to 124)). Combination of *H pylori* infection and NSAIDs use associates with 61.1 times risk of PUD compared to *H pylori* negative individuals with non-

Figure 2 Brain MRI with gadolinium enhancement detects a hypointense pituitary tumour suggestive of a microadenoma (arrow).

NSAIDs use (95% CI 9.98 to 373). In addition, in a population based prospective cohort study,¹¹ tobacco smoking may cause a significant increase in the risk of PUD with dose-response effect (OR=3.8 (95% CI 1.7 to 9.8)).

The relation between corticosteroids and PUD

Although the issue of whether corticosteroid use is associated with an excess risk of PUD is controversial, its independent ulcerogenic action is smaller than that of NSAIDs use, with estimated RR varying from 1.1 (95% CI 0.5 to 2.1)¹² to 2.3 (95% CI 1.4 to 3.7),¹³ based on meta-analyses including patients with underlying diseases predisposing to PUD. However, higher dose of corticosteroid use is likely to more frequently lead to the development of PUD when administered for longer time periods^{13 14} in susceptible patients with previous history of PUD, advanced malignant disease and concurrent NSAIDs use.¹⁵ Especially, the concomitant use of corticosteroids and NSAIDs results in a synergistic increase in the incidence of PUD¹⁶; estimated RR of 4.4 (95% CI 2.0 to 9.7) compared to NSAIDs use alone, and estimated RR of 14.6 (95% CI 6.7 to 32.0) compared to non-users of either drugs.

The relation between corticosteroids and upper GI complications

In large population-based cohort studies, current use of corticosteroids has been associated with an increasing risk for upper GI bleeding (OR=1.8 (95% CI 1.3 to 2.4)) and perforation (OR=1.6 (95% CI 0.9 to 3.1)),¹⁶ and preadmission use of oral corticosteroids is associated with increase in 30-day mortality (adjusted mortality ratio=2.1 (95% CI 1.5 to 3.1)) among patients hospitalised with perforated PUD.¹⁷ The anti-inflammatory effects of corticosteroids may blur symptoms of serious GI disease, causing delayed diagnosis that may account in part for the increased risk of perforated disease associated with their use.¹⁸

Our comments about the present case

In the present case, in the presence of the predisposing background to PUD such as *H pylori* infection and current tobacco smoking, prolonged (at least several months) hypercortisolism might slow down the ulcer healing or be involved in painless ulcer bleeding.

The present case eventually lost 13 kg from his 'original' body weight after the successful transsphenoidal pituitary

adenomectomy. His progressing weight loss since 3-month prior to admission was presumably due to progressing impairment in glucose tolerance (glucose toxicity). Given these considerations, before the patient became symptomatic, he was likely to present with 'unnatural' weight gain secondary to Cushing's disease.

CONCLUSION

In patients with PUD, physician should be alert to the possible endocrine disorders. Especially, even in the absence of any cushingoid appearance, PUD patients suspected of having secondary hypertension or hyperglycaemia should be screened for Cushing's syndrome. In the presence of the predisposing background to PUD, prolonged hypercortisolism may be independently or synergistically involved in the development of PUD. Hypercortisolism may be associated with painless PUD with delayed ulcer healing, which potentially results in serious GI complications.

Learning points

- ▶ In patients with PUD, physician should be alert to the possible endocrine disorders.
- ▶ Especially, even in the absence of any cushingoid appearance, PUD patients suspected of having secondary hypertension or hyperglycaemia should be screened for Cushing's syndrome.
- ▶ In the presence of the predisposing background to PUD, prolonged hypercortisolism may be independently or synergistically involved in the development of PUD.
- ▶ Hypercortisolism may be associated with painless PUD with delayed ulcer healing, which potentially results in serious GI complications.

Competing interests None.

Patient consent Obtained.

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