Acute Hemorrhagic Rectal Ulcer Syndrome: The First Case Series from Thailand

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The term "Acute hemorrhagic rectal ulcer syndrome (AHRUS)" has been denoted as a pathological entity that consists of lower gastrointestinal bleeding with unique clinical features. The common setting can be found in elderly patients who were hospitalized with multiple comorbidities. The typical location is around the dentate line. The predominant feature of these ulcers is profuse and painless rectal bleeding. Currently, this condition has not been established worldwide and it has never been reported in Thailand. The authors reported nine cases of AHRUS. These cases were reviewed from the records of endoscopic procedures which were performed at Siriraj Endoscopy Center between September-December 2006. All underwent complete colonoscopy to evaluate endoscopic appearances. Histopathologic findings were thoroughly reviewed. The characteristics of the ulcers are multiple, round or oval shape located just above the dentate line, with/without evidence of bleeding stigmata. Histopathologic features included superficial necrosis, erosions with acute inflammatory cell infiltration and evidence of recent hemorrhage, all of which were confined to the mucosal layer. No organisms were discovered from the lesions.In conclusion, this is the first review of AHRUS which is an uncommon cause of hematochezia in Thailand. Although this clinical entity is not well established in Western countries, the rising incidence of AHRUS in Asia warrants further investigation into its pathogenesis, treatment and prevention.

Keyword: *Hematochezia, Rectal bleeding, AHRUS*

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Massive bleeding per rectum is not an uncommon condition especially in elderly patients. The most common recognizable causes are diverticula bleeding, angiodysplasia and hemorrhoids.

Acute hemorrhagic rectal ulcer syndrome (AHRUS) is a clinical entity causing hematochezia. This term was proposed by Soeno et al two decades ago. Most of the data were reported in Asia especially from Japan and Taiwan. The entity has not been well established worldwide. Although it has characteristic features, unfortunately, the exact pathogenesis and the effective treatments are still unrevealing. However, this condition has never been established in Thailand.

The authors have observed several cases of massive rectal bleeding from rectal ulcers that were located just above the dentate line. Most of these patients were hospitalized elderly who had multiple comorbidities and the clinical manifestations of bleeding were consistent. These features have drawn our attentions to find the cause of this condition and it turned out that these cases perfectly fit the description of acute hemorrhagic rectal ulcer syndrome (AHRUS). This term has been found in medical literatures rather than in a standard textbook. The authors therefore compiled a case series and reviewed the current relevant literatures.

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Material and Method

A retrospective review of the endoscopic database in Siriraj Endoscopic Center, Mahidol University, was undertaken from September to December of 2006. Only patients who presented with bleeding rectal ulcers were included in this review. The demographic data including age, gender, co-morbid diseases, volume of blood loss and blood transfusion,

usage of antiplatelet and anticoagulant medications, endoscopic findings of the ulcers, therapeutic interventions as well as histopathologic features were collected. The authors excluded the cases that the cause of bleeding could be well-defined.

Results

Between September and December of 2006, nine cases with typical clinical and endoscopic features which are compatible with acute hemorrhagic rectal ulcer syndrome were identified. The male:female ratio was 1:2 and their ages ranged from 59-83years old (Mean 71.7). Every patient had a variety of multiple comorbidities, including hypertension, coronary artery disease, cerebrovascular disease, renal failure, cirrhosis and sepsis. The most common co-morbid disease was type 2 diabetes mellitus. Five out of nine patients (56%) received antiplatelet or anticoagulant treatment. Hypotensive episodes before or during the presence of rectal bleeding were found in more than half of them.

The typical endoscopic findings were multiple, all in round or oval shape. Most of them situated above or around the dentate line. The characteristic of the ulcers could be accompanied by either clean base, overlying clot,visible vessels or spurting vessels (Fig. 1). Treatment modalities were differently applied according to the character of the ulcers. One third of the patients were successfully treated conservatively (*i.e.* no endoscopic intervention) without evidence of rebleeding. Adrenaline (1:10,000) injections were administered in another one third of the patients. Of these, two cases achieved permanent hemostasis while another had rebleeding. The remaining one third of the patients had intractable bleeding despite of the employment of multi-modality interventions including adrenaline (1:10,000) injections, bipolar coagulation and hemoclipping. Five patients received sucralfate enema and the results were inconclusive. Only one patient did not require any blood transfusion. Two of nine died from septicemic shock (patient 5 and 7).

Biopsies of the ulcers could be performed only in 7 patients given that the other two patients had contraindication for biopsy; active and profuse bleeding, impaired coagulation with thrombocytopenia. Histopathologic features were varied in the degrees of mucosal necrosis and recent hemorrhage. Focal to extensive mucosal necrosis with prominent neutrophilic infiltration were common findings. These led to superficial mucosal erosion to deep ulceration into the submucosa. Prominent vascular proliferation, fibrosis and chronic inflammatory cell infiltration could be found in accompanying with the ulcerations (Fig. 2).

Degree of hemorrhage varied from scattered, minute mucosal hemorrhage to substantial areas of mucosal and submucosal hemorrhages. Apart from acute inflammatory cells infiltration, there were no granulomas. Neither acid fast bacilli nor viral inclusions were found in any parts of the specimens.Overall clinical and histological features of all patients were summarized in Table 1.

Discussion

In general, the most common etiologies of lower gastrointestinal bleeding in the geriatric population are diverticular disease and angiodysplasia. With the exception of hemorrhoids, rectal lesions are not frequently mentioned as a differential diagnosis in much of the literature. The most frequently encountered bleeding rectal ulcers are secondary to radiation therapy of the pelvic region (radiation proctopathy), while NSAIDs induced ulcers as well as stercoral ulcers have been rarely reported.

According to the present case review, the authors found that the following features were unique and common:

1) Demographic data: old age, mostly are more than 65 years old. This can be found in both gender.

2) Comorbidities: diabetes mellitus type 2, hypertension, coronary artery disease, cerebrovascular disease, acute renal failure, etc.

3) Clinical features: an abrupt onset of painless and profound rectal bleeding. Most of the bleeding were intractable and almost always necessitating blood transfusion.

4) Endoscopic findings: multiple ulcers commonly located just above the dentate line with various degrees of bleeding stigmata.

5) Histopathologic features: evidence of mucosal necrosis, resulting in mucosal erosion to deep ulceration and hemorrhage.

After a thorough review of the current medical literature, we found that the clinical presentations and findings of the aforementioned characteristics were consistent with “acute hemorrhagic rectal ulcer”. The collective summary of case series were displayed in Table 2. This term has been defined by Soeno et al in 1981 but rarely be seen in a standard textbook. Fujiyama et al described this condition as a syndrome in 1993[1,2]. More recently, the term “acute hemorrhagic rectal ulcer syndrome (AHRUS)” gained more popularity as more reports were later published in Japan and Taiwan[2-5]. In

the Western countries, the similar condition was reported but the term AHRUS has not been recognized. One articles described an identical clinical and endoscopic feature but were named as "benign rectal ulcer with bleeding"[1].

The pathogenesis of AHRUS has not been clearly established. The observation that this syndrome was frequently found in the elderly with multiple comorbidities suggests that atherosclerosis along with diabetes mellitus and hypertension were common risk factors. These conditions may compromise the vascular supply of the rectal mucosa, rendering it susceptible to ischemic damage. Although there were no pre-disposing conditions to acute ischemia such as aortoiliac operation were identified, ischemic process could simply happen owing to low flow stage. Whether the blood supply is acutely disrupted, as in aortoiliac operation or diminished in low flow stages (*i.e.* prolong hypotension), both can lead to the development of rectal ulcers. The latter typically caused prolong immobilization, which Nakamura et al proposed that it may reduce perfusion to the rectal mucosa[6].

Stress has also been proposed as an etiology of AHRUS, but histopathologic findings argue against this hypothesis[3]. The coexistence of stress induced gastric ulcers is unheard of in patient with AHRUS and many cases are generally in stable condition. Furthermore, AHRUS seem to be cluster in elderly while stress related ulcers can occur in any age group.

The unknown etiology of AHRUS emphasizes the importance of delineating it from other conditions that can cause rectal ulcers. In solitary rectal ulcer syndrome (SRUS)[7-9] the patients are younger, usually between 30 and 40 year-old. This group typically presented with a distinct history of chronic constipation, tenesmus, incomplete evacuation, rectal prolapse and even self- digital evacuation. In addition, passage of blood-tinged stools with or without mucus discharge is common. Frank rectal bleeding can occur in a few reported cases. Endoscopic findings of SRUS revealed shallow ulcerative lesions surrounded by hyperemic mucosa. They are typically located on the anterior wall of the rectum, 3-10 cm above the anal verge. Some patients with SRUS may present with a rectal polyp or mass-like lesion in the rectum. Histopathological findings included architectural distortion and fibromuscular obliteration of the lamina propria which can occur from smooth muscle and collagen replacements. The aforementioned features were absent from our review of AHRUS cases.

Ischemic colitis and NSAIDs induced

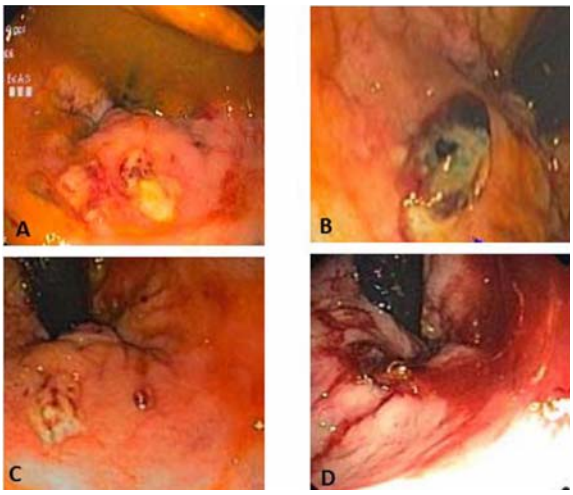

Fig. 1 Various stages of ulcers
A. Clean base ulcers without bleeding
B. Ulcers with non-bleeding vessels
C. Non bleeding visible ulcers status post adrenaline injection
Ulcers with adherent clot andactive oozing blood

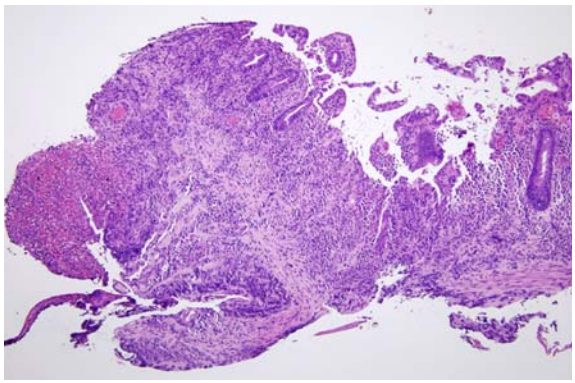

Fig. 2 The histologic findings demonstrates varying degree of mucosal necrosis leading to mucosal erosion (middle part) and ulceration (left side) associated with recent hemorrhage and acute and chronic inflammation

gastrointestinal ulcers may present similarly to AHRUS. In general, however, the rectum is spared in ischemic colitis because of the abundant collateral blood supply from branches of the inferior mesenteric, internal iliac and internal pudendal arteries[10].The term "ischemic colitis" covers a broad range of pathologies, including hyperemic mucosa, submucosal hemorrhage and edema, erosion, ulceration and gangrene. Rectum was involved in 5-6% of ischemic colitis cases[9-12]. A review of case series of bleeding rectal ulcers by Fasiha Kanwal et al suggested that ischemia was the etiology in only

Table 1. Clinical features and histological findings of 9 patients with AHRUS in the currentserie

Pt	Age	Sex	Co-morbid diseases	Antiplatelet/ anticoagulant	Hypo Tension	Units of Blood Transfused	Number of Ulcers	Endoscopic Intervention	Histopathology	Recurrent bleeding	Outcome
1	69	F	DM,septicemia	No	Yes	5 u	Multiple	Adrenaline inj.	Superficial mucosal erosion, minimal mucosal hemorrhage	Yes	Survived
2	75	F	HT, CAD, UTI, pneumonia	Yes	No	1 u	Multiple	No	Superficial mucosal erosion and ulceration, hemorrhage admixed with acute inflammatory cells	No	Survived
3	59	F	DM, HT, ARF, Dyslipidemia	No	Yes	4 u	Multiple	No	Superficial mucosal erosion, hemorrhage admixed with acute inflammatory cells	No	Survived
4	67	M	DM, HT, CVA UTI	Yes	Yes	9u	Multiple	Adrenaline inj, gold probe, hemoclip	Mucosal ulceration, dense acute inflammatory cell infiltration	Yes	Survived
5	75	F	DM, HT, ARF, Dyslipidemia	Yes	No	6 u	Multiple	Adrenaline inj., hemoclip	Superficial mucosal erosion and ulceration, hemorrhage admixedwith acute inflammatory cells	Yes	Dead (septicemia)
6	72	M	DM, HT, CRF on PD CAD s/p PTCA	Yes	Yes	4 u	Multiple	Adrenaline inj.	N/A	No	Survived
7	72	F	DM, HT, CAD, ARF	Yes	Yes	1 u	Multiple	Adrenaline inj.	Superficial mucosal erosion, hemorrhage admixed with acute inflammatory cells	No	Dead (pneumonia with sepsis)
8	74	M	HT, CVA, CAD	Yes	No	none	Multiple	No	Ulceration, dense acute inflammatory cells infiltration, minimal mucosal hemorrhage	No	Survived
9	83	F	Cirrhosis	No	Yes	12 u	Multiple	Hemoclip	N/A	Yes	Survived

Abbreviation: F = Female M = Male DM = Diabetes mellitus HT = Hypertension CAD = Coronary artery disease UTI = Urinary tract infection ARF = Acute renal failure CRF = Chronic renal failure PD = Peritoneal dialysis. LOS = Length of stay

Table 2. Collective summary of the relevant literatures

Author	Ref	Year	N	Co-morbid	Hypo tension	Blood Tx	No. of ulcer	Intervention Methods	Histopathology	Outcome
Chan-An Tseng et al	1	2004	19	CVA, DM, sepsis, renal failure, liver failure, cancer	+2/19, -17/19	Yes	Solitary 8/19, multiple 11/19, various degree	Electrocautery 4/19, suture ligation 3/19, gauze temponade 11/19Pure ethanol inj 1/19	14/19 necrosis with denudation of covering epithelium, hemorrrhage, and multiple thrombi in the vessels ofthe mucosa and underlying stroma	9/19 Survived, 10/19 died.
Hsin-Yuan Huang et al	3	2006	26	CVA, CRF, DM, CAD, cirrhosis, cancer, sepsis	N/A	Yes	18/26 solitary, 8/26 multiple	5/26 EndoscopioPx, 2/26 embolization. 26/26 Per anal suture ligation	N/A	14/26 survived, 11/26 died, 1/26 N/A.
Kunio Takeuchi et al	4	2001	4	Cancer, CVA	N/A	N/A	Solitary 4/4	1 conservative Px, 1 clipping+ per anal ligation 2/4 N/A	1/4 invasion of inflammatory cells, mainly neutrophils, granulation tissue augmenting capillaries, and some cryptoepithelium. 3/4 N/A	N/A
Takatomi Oku et al	5	2006	20	NS, CVA, DM, HT, CAD, CHF, cancer, bony fracture, aortic aneurysm, PAN, ASO, pneumonia, ITP, RA, PBC	N/A	N/A	17/20 solitary, 3/20 multiple	13/20 clipping, 1/20 APC, 2/20 clipping + APC, 1/20 clipping + ethanol inj 1/20 APC + ethanol inj 1/20 thrombin spray 1/20 observation	N/A	15/20 survived, 5/20 died.
R.J.Hendrickson et al	2	2003	4	HT, DM, ARF, CHF, ABE, CAD, ESRD, VHD and AF, GBS	1/4 Yes, 3/4 N/A	3/4 Yes 1/4 N/A	1/4 solitary 1/4 multiple 2/4 N/A	1/4 coagulation 2/4 surgery, 1/4 embolization	1/4 no tumor and extensive ulceration with acute and chronic inflammation, 1/4 acute and chronic inflammation, 2/4 N/A	N/A
This series		2006	9	DM, HT, CAD, CVA, septicemia, pneumonia, ARF, UTI, cirrhosis	6/9 Yes, 3/9 No	8/9 Yes, 1/9 No	Multiple	3/9conservative, 3/9 Adrenaline inj., 3/9 Adrenaline inj.+ bipolar coagulation+ clipping.	7/9 *2/9 N/Arecent hemorrhage and mucosal necrosis infiltrated by dense neutrophilic infiltration leading to superficial mucosal erosion to deep ulceration	7/9 survived, 2/9 died.

one of 23 patients[11]. This argued against hemorrhagic rectal ulcers as a feature of ischemic colitis.

NSAIDs are notorious in producing ulcers of the gastric and small intestinal mucosa and less commonly colonic mucosa[9,12] Koichi Kurahara et al reported 14 cases of NSAIDs induced colonic ulcerations[9,12]. One half of them involved multiple sites while most were limited to ileocecal area. Few had an isolated ulcer located on the sigmoid or transverse colon. Only two cases who received suppository forms of NSAIDs had a solitary ulcer in the rectum close to the anal ring and were accompanied by an ulcer at the ileocecal valve. Unlike endoscopy, histology can help differentiate ischemic colitis and NSAIDs induced rectal ulcers from AHRUS. For instance, both ischemic colitis and NSAIDs-induced colitis have similar histological features that range from focal de-epithelization of superficial mucosa, mucosal atrophy, fibrosis of the lamina propria to mucosal necrosis and eosinophils merging into the lamina propria[10,13]. On the other hand, the histological features of AHRUS include acute inflammatory cell infiltration and complete architectural destruction in the necrotic area accompanied by hemorrhage.

Stercoral ulcer scan also cause rectal bleeding as a result of pressure necrosis from fecal impaction. The patients usually had a history of constipation. Colonic perforations can occur from the ulcers, which is commonly located on the sigmoid colon and rectum. Endoscopic findings of stecoral ulcers are not well addressed since hematochezia is an uncommon presentation and therefore, colonoscopy or sigmoidoscopy is not routinely indicated. Knigge et al described a case of stercoral ulcer, which a visible vessel was found in the rectum[14]. They noted a fragment of solid stool that conformed to the margins of the ulcer near the lesion. The finding supports the diagnosis of stercoral ulcer. The bleeding ceased with adrenaline injection and bipolar coagulation. Table 3 presented features of different types of rectal ulcers.

Endoscopic features of AHRUS varied widely. Takatomi Oku et al denied any specific trend either in location or number of the ulcers[3]. They also classified the endoscopic appearance of the ulcers into three types, namely, nearly round, irregular and Dieulafoy-like lesion. In present case series, the bleeding rectal ulcers can be categorized into clot adherent, non-bleeding visible vessel and spurting vessel types, similar to the classification of bleeding peptic ulcers. Such classification facilitates to determine an appropriate choice of endoscopic intervention. The

Table 3. Features of different types of rectal ulcer

Types of ulcer	Age group	Clinical presentation	Endoscopic findings	Histologic findings
AHRUS	Old age, mostly > 65	Painless/profound rectal bleeding, commonly associated with hypotension	Can be varied from clean base, clot adherence, visible vessels and spurting	Various degrees of mucosal necrosis and recent hemorrhage. Predominant neutrophil infiltration
Ischemic colitis	Old age	Blood tinge stools ± mucous discharge	Geographic appearance, mostly involved watershed area. Rectum can be affected 5-6%	Focal de-epithelization of superficial mucosa, mucosal atrophy, fibrosis of the lamina propria to mucosal necrosis and eosinophils merging into the lamina propria
NSAIDs induced colonic ulceration	Any age group,	NSAIDs exposure, vary in clinical presentation	Multiple sites, most were limited to ileocecal area.	Similar findings as ischemic colitis
SRUS	30-40	Chronic constipation, tenesmus, digital evacuation	Shallow ulcerations or polypoid lesion, typically on the anterior wall of the rectum.	Architectural distortion and fibromuscular obliteration of the lamina propria.
Stercoral ulcer	Younger age	Chronic constipation	Not well defined. A fragment of stool conformed to the ulcer margin.	N/A

success rate and risks of rebleeding cannot be evaluated due to the small number of patients.

Endoscopic treatment has been challenging given that this condition typically affects critically ill patients. An experienced endoscopist might be required to achieve permanent hemostasis. Embolization which is commonly used to control small bowel bleeding, may not be appropriate for rectal ulcer bleeding. Literatures on using arterial embolization to treat bleeding rectal ulcers showed inconclusive results in both success and failure sides[1,15]. Another alternative offered by Hung et al is per anal suturing via an anoretractor as a rapid means of controlling bleeding[5]. It can be performed safely and efficiently at bedside, which is very crucial for the critically ill patients. Unfortunately, the disadvantage is the high recurrent bleeding in the first few days (eleven out of 26 patients). Rebleeding has been correlated with the disease severity and coagulopathy. The scant number of literature on different hemostatic techniques highlights the need for double blinded randomized controlled trials to elucidate the best therapeutic modality.

In conclusion, this is the first case series of AHRUS in Thailand that confirms the existence and importance of AHRUS. Raising the awareness on AHRUS is important so that physicians include it in the differential diagnosis of any bleeding rectal lesion. Further research studies are necessary to understand the pathogenesis and revise a proper classification of ulcers, which will be a guide to the most suitable means of prevention and management.

Potential conflicts of interest

None.

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กลุ่มอาการแผลเลือดออกเฉียบพลันบริเวณลำไส้ตรง: รายงานผู้ป่วยแรกในประเทศไทย

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กลุ่มอาการแผลเลือดออกเฉียบพลันบริเวณลำไส้ตรง (Acute hemorrhagic rectal ulcer syndrome-AHRUS) บ่งถึงภาวะเลือดออกจากทางเดินอาหารส่วนล่างที่มีลักษณะเฉพาะทางคลินิกคือ พบในผู้ป่วยสูงอายุในโรงพยาบาล ผู้ป่วยมักมีโรคร่วมหลายโรค ตำแหน่งของแผลมักพบบริเวณ dentate line ลักษณะเด่นของภาวะดังกล่าวคือ มีเลือดออกปริมาณมากโดยไม่มีอาการเจ็บร่วมด้วย ปัจจุบันกลุ่มอาการนี้ยังไม่เป็นที่รู้จักกันแพร่หลายนักและยังไม่เคยมีรายงานในประเทศไทยมาก่อน คณะผู้นิพนธ์ได้ทำการทบทวนกรณีศึกษารวมทั้งสิ้น 9 ราย โดยรวบรวมจากรายงานผลการส่องกล้องศูนย์ส่องกล้องทางเดินอาหารวีกิจวีรานุวัตติ์ โรงพยาบาลศิริราช ในระยะเวลา 3 เดือน (กันยายน–ธันวาคม พ.ศ. 2549) ผู้ป่วยทุกรายได้รับการบันทึกอาการอาการแสดงผลการตรวจทางห้องปฏิบัติการ รวมถึงข้อมูลสำคัญในทางคลินิก ผลการส่องกล้องตรวจทางเดินอาหารส่วนล่าง ที่ประเมินดูลักษณะที่พบจากการส่องกล้องรวมถึงผลการตรวจชิ้นเนื้อทางพยาธิวิทยา

ลักษณะจำเพาะของแผลที่พบได้แก่ มักมีหลายแผล รูปร่างของแผลอาจเป็นแผลกลมหรือรูปไข่ อาจพบลักษณะ ที่บ่งถึงภาวะแผลเลือดออกเฉียบพลันร่วมด้วย ตำแหน่งของแผลทุกรายพบเหนือต่อ dentate line ลักษณะของแผล จากการตรวจด้วยกล้องจุลทรรศน์พบเนื้อตายและเลือดออกในบริเวณเยื่อบุผิวลำไส้ใหญ่ เกิดเป็นแผลตื้นๆ ร่วมกับ มีกลุ่มเซลล์อักเสบ และตรวจไม่พบเชื้อก่อโรค

สรุป กลุ่มอาการแผลเลือดออกเฉียบพลันจากบริเวณลำไส้ตรง เป็นสาเหตุของภาวะเลือดออกจากทางเดินอาหาร ส่วนล่างที่พบได้ไม่บ่อย การทบทวนกรณีศึกษาฉบับนี้เป็นการรายงานครั้งแรกในประเทศไทย แม้ภาวะดังกล่าวจะไม่เป็นที่รู้จักกันแพร่หลายนักโดยเฉพาะในประเทศทางตะวันตก อย่างไรก็ตามอุบัติการณ์ที่เพิ่มขึ้นของภาวะดังกล่าว ในเอเชียบ่งชี้ว่าแพทย์ควรให้ความสนใจและศึกษาค้นคว้าเพิ่มเติมมากขึ้น ทั้งในด้านพยาธิสรีรวิทยา การรักษาที่มีประสิทธิภาพ และการป้องกันการเกิดโรค