

# Case Report

## Ehlers-Danlos Syndrome Type IV with Gastric Adenocarcinoma

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**Background:** Ehlers-Danlos syndrome has many subtypes. The vascular type (type IV) is characterized by thin, translucent skin, easy bruising, characteristic facial appearance, and arterial, intestinal, and/or uterine fragility.

**Objectives:** To encourage a better understanding of vascular EDS as a basis for early diagnosis, prevention, and management of complications. A first case of EDS type IV with adeno-carcinoma of the stomach in Thailand was reported and literature was reviewed.

**Result:** A 62-year-old Thai priest was admitted in Priest Hospital because of progressive muscle weakness of both legs with neurogenic claudication from compression fracture of L1-2. Abdominal aortic aneurysm were detected with upper gastrointestinal hemorrhage, esophagogastroduodenoscopy showed diffuse gastric body swelling and erythema resulting in chronic gastritis. Gastric biopsy was indicative of adenocarcinoma of the stomach and gastrectomy was done. Dermatologists were consulted due to generalized cutaneous pain, easy bruising following venepuncture, and EKG padding. A vascular EDS type IV was diagnosed.

**Conclusion:** After gastrectomy, the patient became drowsy and unconscious from profuse recurrent cerebral hemorrhage and expired.

**Keywords:** Ehlers-Danlos syndrome type IV, Vascular Ehlers-Danlos, COL3A1 gene, Arterial rupture

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Ehlers-Danlos syndrome (EDS) is a rare heterogeneous group of inherited disorder of connective tissue predominantly comprised of collagen. In 1986, the International Nosology of Heritable Disorders of connective Tissue redefined EDS into subtypes I-VIII and X with certain phenosubtypes (EDS I and II) that overlap<sup>(1)</sup>.

Unique in other forms, EDS type IV so-called vascular type result of mutation in the gene *COL3A1* encoding for type III pro-collagen synthesis<sup>(1-5)</sup>. There is currently no effective medical treatment that can predictably decrease the risk of vascular complications

and increase life expectancy in these patients. Operative treatment is indicated at the presence of frank or imminent life threatening bleeding. In part to its rarity, clinical experience is lacking and the diagnosis is often made after a catastrophic complication incident. It is mostly autosomal dominantly inherited although there have been reports of recessive transmission and sporadic case<sup>(6-9)</sup>.

Diagnosis of EDS type IV is based on two of the four clinical criteria: easy bruising, thin skin with visible veins, characteristic facial features, and the rupture of arteries, uterus, or intestines and confirmed by the demonstration that cultured fibroblasts synthesize abnormal type III pro-collagen molecules or by the identification of a mutation in the gene encoding for type III pro-collagen (*COL3A1*)<sup>(2,3)</sup>. Unique

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in other forms, EDS type IV may lead to premature death from spontaneous arterial, intestinal, or uterine rupture<sup>(10,11)</sup>.

Although there are many brief descriptions, in part to its rarity, clinical experience is lacking and the diagnosis is often made only after a catastrophic complication or a postmortem examination. To encourage better understanding basis for vascular EDS for early recognition, the first case of EDS type IV with adenocarcinoma of the stomach in Thailand was reported with review of literatures.

### Case Report

A 62-year-old Thai priest was hospitalized at the Priest Hospital in Bangkok in July 2005 due to progressive muscle weakness of both legs for 2 months. The symptom was severe and made him unable to walk. Two years prior to this admission, he experienced chronic low back pain and frequently coped with neurogenic claudication while walking long distance. Anterior collapse of L2 body and compression fracture with narrow L1-L2 disc space, along with a coincidental distal abdominal aortic aneurysm was detected. Apart from those events, he suffered upper gastrointestinal hemorrhage. The esophagogastroduodenoscopic findings showed diffuse gastric body swelling and erythema resulting in chronic gastritis from pathological reading. Dermatologists were consulted due to the problems of generalized cutaneous pain, easy bruising following venepuncture, and EKG padding. Specific investigations were performed to assess underlying connective tissue disorder.

Due to long-term of being priest, the patient had no immediate family to contact but recalled that two out of three of the paternal relatives of unknown order died suddenly from profuse bleeding per oral at age of 13 and 30, and the other died from sudden cardiac arrest at age of 60.

The family pedigree as far as the patient could trace back is shown in Fig. 1. The clinical pictures were show in Fig. 2.

The patient's medical history was unremarkable for medical underlying diseases and trauma

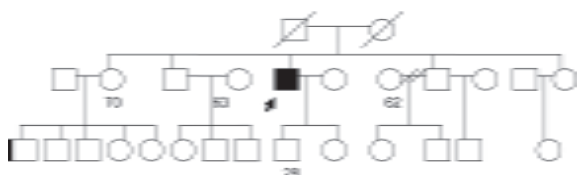


Fig. 1 Family pedigree of the patient

although he admitted taking herbal medicine for pain from various sources once in a while during the last decade.

A systematic review was significant for a frail male with translucent skin and bruises. On physical examinations, he posed normal Asian appearance. His height was 165 cm with an upper: lower limb ratio 75:80 cm. He had generalized thin, translucent skin enabling striking visualization of a network of superficial veins

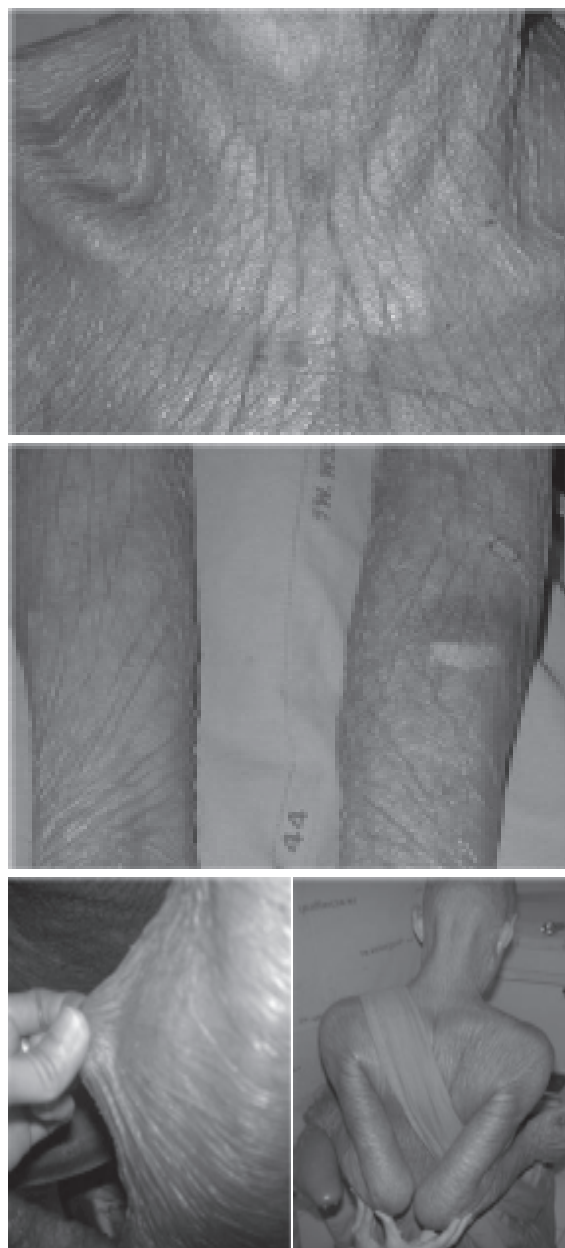


Fig. 2 Clinical pictures of the patient

on the neck, chest, and proximal extremities. Apart from this, there were discrete purpuric patches and small hematomas on both forearms, and one eroded indurated purpuric patch on the anterior chest wall, which corresponded to venepuncture and EKG lead sites. Old scars appeared depigmented and atrophic. Except for the face, the skin was tender, very loose, and thin with velvety texture with positive transillumination, and slightly elastic with normal recoil. He had aged appearance to the extremities, particularly the hands. The vital signs were unremarkable and blood pressure was equal on all extremities. A pulsatile and slightly tender mass (6 centimeters) was palpated just above the umbilicus and generated a bruit on auscultation. The patient also displayed mild hyperextensibility of the shoulder, wrists, and phalangeal joints by performing a positive elbow-to-elbow test, and was able to touch his umbilicus with the right hand passed around the back and approaching the umbilicus from the left. A grade III paraplegia of both lower extremities was also detected on examination.

Laboratory test results were unremarkable except for mild elevated aspartate aminotransferase (74 U/L; normal 5-40 U/L). Skin biopsy of both normal skin and atrophic scar showed thin and atrophic epidermis with very loose and thin dermis. Masson trichrome showed diminished mature collagen while Verhoeff van Gieson stain for elastin expressed fragmentation of elastic fiber. Further investigation of chronic back and abdominal pain were done with MRI disclosing a compression fracture of L2 body without mass effect with distal abdominal aortic aneurysm. Whole abdominal ultrasonography suggested fusiform type of abdominal aortic aneurysm with suspected dissection, one right hyperechoic nodule, suspected hemangioma, one large right and one small left renal cyst, respectively. Cranial CT scan revealed an old 5 millimeters hematoma of the insula lobe.

During hospitalization, the patient felt unrelenting epigastric discomfort and anorexia. Gastroscopy was repeated and demonstrated marked edema of the gastric walls with minimal bleeding. A subsequent gastric biopsy was indicative of adenocarcinoma of the stomach. Along the course, the patient was suspected of an underlying vascular type of Ehler Danlos so culture of dermal fibroblast was done to confirm abnormal quantity and quality of type III collagen production. Despite the suspicion of an underlying connective tissue disorder, especially EDS type IV, in which surgery could be fatal due to friable vessels and poor healing, the gastric carcinoma causing

obstruction of the pylorus was urgent problem that made surgical intervention mandatory. In addition, the dissecting abdominal aneurysm needed to be considered. This decision was a dilemma for surgeons for the mortality of the malignancy had to be weighed with the high risk of surgery. During gastrectomy, the surgeons encountered friable tissue and difficulty in suturing the wounds. The following day, the patient became drowsy and unconscious from profuse cerebral hemorrhage, which recurred shortly and he eventually expired.

### Discussions

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited disorder of connective tissue. Estimates of the prevalence of the vascular type of EDS vary from 1:100,000 to 1:1,000,000<sup>(6)</sup>. However, no exact prevalence from Thailand has been reported.

Usually patients go unrecognized symptom. The hallmarks of EDS are fragility of the skin and blood vessels, hyperextensibility of the skin, and joint hypermobility<sup>(12)</sup>. In 1986, the International Nosology of Heritable Disorders of connective Tissue redefined EDS into subtypes I-VIII and X. Clinically certain phenosubtypes ( EDS I and II) overlap and some patients do not neatly fall into one category<sup>(1)</sup>. Nowadays progress in molecular biology enables further subdivision of some types.

EDS type IV, so-called vascular type, is a rare and mostly autosomal dominantly inherited although there has been reports of recessive transmission and sporadic cases<sup>(6-9)</sup>. The disorder results from mutation in the gene *COL3A1* encoding for type III pro-collagen synthesis<sup>(13,14)</sup>. About 50% of affected individuals have inherited the mutant *COL3A1* gene on chromosome 2q31 from an affected parent and about 50% have new disease-causing mutation<sup>(9,15)</sup>. *COL3A1* gene leads to type III pro-collagen production that is one of the parts of connective tissue throughout the whole body. Mutation on this gene causes abnormal connective tissue elasticity of skin, soft tissue, intestine, uterus, and vessels.

The characteristic facial features include thin, delicate pinched nose and prominent bones and eyes. The skin is thin, easily bruised, and has a tendency to form hematomas. Although not hyperextensible, the skin is translucent and has highly visible superficial veins more apparent in the shoulders, chest, and abdomen. Joint laxity is mild involving small joints<sup>(17)</sup>. Other features include acrogeria, tendon/muscle

rupture, congenital dislocation of hips, talipes equinovarus, and gingival recession<sup>(9)</sup>. Thus, the distribution of type III pro-collagen predominantly in the skin, blood vessel walls, and hollow organs explains its clinical manifestations.

The histology in EDS is variable and often within normal limits. Typically, a loose, disordered dermal collagen network can be found. Elastic fibers are usually increased and orientated irregularly<sup>(18,19)</sup>. While clinical diagnosis is highly indicative of the disease, laboratory confirmation is more conclusive and strongly recommended if available<sup>(2)</sup>. The diagnosis is confirmed by the demonstration that cultured fibroblasts synthesize abnormal type III procollagen molecules or by the identification of a mutation in the gene encoding for type III procollagen (*COL3A1*)<sup>(1-5)</sup>. More simply, the measurement of pro-collagen propeptides in body fluids offers a direct method to monitor human collagen synthesis<sup>(20-22)</sup>. The serum concentrations of PIIINP in EDS patients have been shown to be abnormally low or in low normal range with good correlation to the ability of the patients' cultured fibroblast to secrete type III procollagen<sup>(23)</sup>. However, the elimination of PIIINP molecules from the serum is a constant process and may be altered, e.g. by abnormal liver function. Hence, the concentration of PIIINP in the interstitial fluid (SBF) more accurately reflects an individual's synthesis of type III collagen.

Skin specimen from the patient for fibroblast culture was sent to the Collagen Diagnostic Laboratory, University of Washington, Department of Pathology, for analysis. The cultured fibroblasts demonstrated normal synthesis and secretion of types I and III procollagen and their conversion to collagen. Whereas biochemical testing for the vascular type of EDS probably identifies more than 95% of the individuals with structural alterations in the protein synthesized, it may be less sensitive in identifying vascular EDS as a result of a consequence of mutations that decrease production<sup>(10,24)</sup>. Analysis of type III pro-collagen synthesized by cultured cells identifies an abnormality in chain mobility, while sequence of *COL3A1* cDNA provides a substrate for mutation detection<sup>(9)</sup>.

Direct analysis of *COL3A1* gene provides an alternative approach when a blood sample or other source of genomic DNA is the only sample available. When this approach is used, some classes of mutations may be missed, particularly small genomic deletions of single or multiple exons. Protein-based studies may be less sensitive for the identification of mutations that decrease production but do not alter struc-

ture of type III pro-collagen, as has been reported<sup>(25,26)</sup>.

During treatment, arteriography should be avoided whenever possible, but noninvasive imaging studies (echocardiogram, carotid and abdominal ultrasound scanning, CT or MRA) provide an excellent means of evaluating the presence and extent of complications<sup>(17)</sup>.

Non-invasive modern B-mode ultrasound techniques can be used to demonstrate thin skin, characteristic of EDS, in place of skin biopsy<sup>(27)</sup>. In addition, measurement of pro-collagen propeptides is a valuable non-invasive method, which is helpful in the diagnosis and classification of EDS.

Prenata testing is clinically available for fetuses at 50% risk families in which the underlying biochemical abnormality of type III collagen or the disease-causing mutation in *COL3A1* has been identified. Diagnosis should be considered in youngsters with unexplained arterial rupture or dissections, particularly in families with history of similar events although 50% of affected individuals have a de novo disease-causing mutation<sup>(9)</sup>. This may be the case in our patient, who does not exactly seem to inherit this disorder dominantly. A possible non-medical explanation, which cannot be excluded, is alternate paternity or undisclosed adoption.

Complications of EDS type IV are rare during childhood, but approximately 80% of patients have already experienced at least one complication by the age of 40<sup>(10)</sup>. Patients are unaware of the diagnosis until they present, with the spontaneous arterial rupture or dissection, mostly arising from an underlying true fusiform or false aneurysm<sup>(17)</sup>. Spontaneous vascular, uterine, and intestinal ruptures may lead to premature death in EDS type IV as opposed to other forms<sup>(10,11)</sup>. No correlation between the nature or location of the mutation and type or frequency of major complications has been discerned however<sup>(16)</sup>.

Differential diagnosis includes other forms of EDS should be considered in individuals with easy bruising, joint hypermobility, or chronic joint dislocation who have normal collagen III biochemical studies. The disorders in which clinical findings overlap with the vascular type of EDS include the following: EDS, classic type, EDS kyphoscoliotic, EDS type VIII periodontal, isolated arterial aneurysm, Loeys-Dietz syndrome, localized trauma and collagen vascular disease, polycystic kidney disease(AD), Marfan Syndrome, PXE, hereditary hemorrhagic telangiectasia. The reported patient however does not fall in any of these categories.



There is currently no effective medical treatment that can predictably decrease the risk of vascular complications and increase life expectancy in EDS-IV patients. Operative treatment is indicated in patients with frank or imminent life threatening bleeding<sup>(28,29)</sup>.

Although operative mortality was not excessively high, the incidence of postoperative bleeding complications and late graft-related problems was significant. In addition, despite successful repair of vascular complications, survival was shortened because of secondary vascular or graft-related complications and anastomotic disruption with attempted operation repair<sup>(17)</sup>.

## References

1. Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, et al. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. *Am J Med Genet* 1988; 29: 581-94.
2. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* 1998; 77: 31-7.
3. Barabas AP. Heterogeneity of the Ehlers-Danlos syndrome: description of three clinical types and a hypothesis to explain the basic defect(s). *Br Med J* 1967; 2: 612-3.
4. Barabas AP. Vascular complications in the Ehlers-Danlos syndrome, with special reference to the "arterial type" or Sack's syndrome. *J Cardiovasc Surg (Torino)* 1972; 13: 160-7.
5. Pope FM, Martin GR, Lichtenstein JR, Penttinen R, Gerson B, Rowe DW, et al. Patients with Ehlers-Danlos syndrome type IV lack type III collagen. *Proc Natl Acad Sci U S A* 1975; 72: 1314-6.
6. Pope FM, Nicholls AC, Jones PM, Wells RS, Lawrence D. EDS IV (acrogeria): new autosomal dominant and recessive types. *J R Soc Med* 1980; 73: 180-6.
7. Sulh HM, Steinmann B, Rao VH, Dudin G, Zeid JA, Slim M, et al. Ehlers-Danlos syndrome type IV D: an autosomal recessive disorder. *Clin Genet* 1984; 25: 278-87.
8. Pope FM, Martin GR, McKusick VA. Inheritance of Ehlers-Danlos type IV syndrome. *J Med Genet* 1977; 14: 200-4.
9. Pepin MG, Byers PH. Ehlers-Danlos syndrome, vascular type. *GeneReviews*. 2006 [cited 2007 Jul 20]. Available from: <http://www.geneclinics.org/profiles/eds4/details.html>.
10. Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000; 342: 673-80.
11. North KN, Whiteman DA, Pepin MG, Byers PH. Cerebrovascular complications in Ehlers-Danlos syndrome type IV. *Ann Neurol* 1995; 38: 960-4.
12. Beighton P. The Ehlers-Danlos syndrome. London: Heinemann; 1970.
13. Pope FM, Narcisi P, Nicholls AC, Germaine D, Pals G, Richards AJ. COL3A1 mutations cause variable clinical phenotypes including acrogeria and vascular rupture. *Br J Dermatol* 1996; 135: 163-81.
14. Superti-Furga A, Gugler E, Gitzelmann R, Steinmann B. Ehlers-Danlos syndrome type IV: a multi-exon deletion in one of the two COL3A1 alleles affecting structure, stability, and processing of type III procollagen. *J Biol Chem* 1988; 263: 6226-32.
15. Smith LT, Schwarze U, Goldstein J, Byers PH. Mutations in the COL3A1 gene result in the Ehlers-Danlos syndrome type IV and alterations in the size and distribution of the major collagen fibrils of the dermis. *J Invest Dermatol* 1997; 108: 241-7.
16. Jansen T, Paepe AD, Nuytinck L, Altmeyer P. Acrogeric phenotype in Ehlers-Danlos syndrome type IV attributed to a missense mutation in the COL3A1 gene. *Br J Dermatol* 2001; 144: 1086-7.
17. Oderich GS, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. *J Vasc Surg* 2005; 42: 98-106.
18. Sulica VI, Cooper PH, Pope FM, Hambrick GW Jr, Gerson BM, McKusick VA. Cutaneous histologic features in Ehlers-Danlos syndrome: study of 21 patients. *Arch Dermatol* 1979; 115: 40-2.
19. Pierard GE, Pierard-Franchimont C, Lapiere CM. Histopathological aid at the diagnosis of the Ehlers-Danlos syndrome, gravis and mitis types. *Int J Dermatol* 1983; 22: 300-4.
20. Oikarinen A, Autio P, Kiistala U, Risteli L, Risteli J. A new method to measure type I and III collagen synthesis in human skin in vivo: demonstration of decreased collagen synthesis after topical glucocorticoid treatment. *J Invest Dermatol* 1992; 98: 220-5.
21. Autio P, Oikarinen A, Melkko J, Risteli J, Risteli L. Systemic glucocorticoids decrease the synthesis of type I and type III collagen in human skin in vivo, whereas isotretinoin treatment has little

- effect. *Br J Dermatol* 1994; 131: 660-3.
22. Risteli J, Niemi S, Trivedi P, Maentausta O, Mowat AP, Risteli L. Rapid equilibrium radioimmunoassay for the amino-terminal propeptide of human type III procollagen. *Clin Chem* 1988; 34: 715-8.
  23. Steinmann B, Superti-Furga A, Joller-Jemelka HI, Cetta G, Byers PH. Ehlers-Danlos syndrome type IV: a subset of patients distinguished by low serum levels of the amino-terminal propeptide of type III procollagen. *Am J Med Genet* 1989; 34: 68-71.
  24. Schwarze U, Schievink WI, Petty E, Jaff MR, Babovic-Vuksanovic D, Cherry KJ, et al. Haploinsufficiency for one COL3A1 allele of type III procollagen results in a phenotype similar to the vascular form of Ehlers-Danlos syndrome, Ehlers-Danlos syndrome type IV. *Am J Hum Genet* 2001; 69: 989-1001.
  25. Kuivaniemi H, Prockop DJ, Wu Y, Madhathi SL, Kleinert C, Earley JJ, et al. Exclusion of mutations in the gene for type III collagen (COL3A1) as a common cause of intracranial aneurysms or cervical artery dissections: results from sequence analysis of the coding sequences of type III collagen from 55 unrelated patients. *Neurology* 1993; 43: 2652-8.
  26. Tromp G, Wu Y, Prockop DJ, Madhathi SL, Kleinert C, Earley JJ, et al. Sequencing of cDNA from 50 unrelated patients reveals that mutations in the triple-helical domain of type III procollagen are an infrequent cause of aortic aneurysms. *J Clin Invest* 1993; 91: 2539-45.
  27. Autio P, Turpeinen M, Risteli J, Kallioinen M, Kiistala U, Oikarinen A. Ehlers-Danlos type IV: non-invasive techniques as diagnostic support. *Br J Dermatol* 1997; 137: 653-5.
  28. Germain DP. Clinical and genetic features of vascular Ehlers-Danlos syndrome. *Ann Vasc Surg* 2002; 16: 391-7.
  29. Bergqvist D. Ehlers-Danlos type IV syndrome. A review from a vascular surgical point of view. *Eur J Surg* 1996; 162: 163-70.

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## รายงานผู้ป่วย Ehlers-Danlos syndrome ชนิดที่ 4 ที่มี Adenocarcinoma ของกระเพาะอาหาร

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**ภูมิหลัง :** กลุ่มอาการ Ehlers-Danlos (EDS) ประกอบด้วยชนิดย่อยหลายประเภท EDS ชนิดที่ 4 ผู้ป่วยจะมีอาการผิวหนังบาง มีจ้ำเลือดออกใต้ผิวหนังได้ง่าย หน้ามีลักษณะเฉพาะ และเส้นเลือดภายในอวัยวะแตกได้ง่าย

**วัตถุประสงค์ :** เพื่อให้เข้าใจ EDS ชนิดที่ 4 ได้ดีขึ้นในแง่การวินิจฉัย การรักษา การป้องกันภาวะแทรกซ้อน จึงขอรายงานผู้ป่วย EDS ชนิดที่ 4 รายแรกในประเทศไทย ที่มีโรคมะเร็งของกระเพาะอาหารชนิด Adenocarcinoma ร่วมด้วย

**ผลการรักษา :** ผู้ป่วยพระสงฆ์ชาวไทย อายุ 62 ปีมารับการรักษาในโรงพยาบาลสงฆ์ เพราะขาไม่มีแรง เดินไม่สะดวก เพราะมีกระดูกสันหลังหักแบบกดทับระดับ L1-2 , มีเส้นเลือด Aorta ภายในท้องโป่งพอง มีเลือดออกในทางเดินอาหารส่วนบน ส่งกล้องดูพบว่ามีแผลรื้อรังในกระเพาะอาหารและมีเส้นเลือดฝอยมารวมตัวกัน ตัดชิ้นเนื้อดูพบว่าเป็นมะเร็งในกระเพาะอาหารชนิด Adenocarcinoma เนื่องจากพระสงฆ์มีเลือดออกง่ายบริเวณผิวหนัง แพทย์โรคผิวหนังมาตรวจและตรวจพิเศษ สรุปได้ว่าเป็น EDS ชนิดที่ 4 และเข้ารับการผ่าตัดกระเพาะอาหาร

**สรุป :** หลังผ่าตัดผู้ป่วยมีเลือดออกในสมองมาก และควบคุมไม่ได้ จึงเสียชีวิต

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