

Primary Adenocarcinoma of Anal Fistula: A Case Report and Literature Review

Boonnithi W, MD¹, Lohsiriwat V, MD, PhD¹

¹ Colorectal Surgery Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

The authors described an uncommon case of 64-year-old male with mucinous adenocarcinoma arising in a long-standing anal fistula. After an appropriate staging, en bloc abdominoperineal resection with distal sacrectomy and myocutaneous flap reconstruction was performed. Post-operative period was uneventful. Pathological examination showed mucinous adenocarcinoma arising in anal fistula and invading the cortex, medulla of sacrum, and surrounding soft tissue. All surgical margins were free and there was no nodal metastasis. The patient had no evidence of recurrence after 2-year follow-up. The present paper reported a successful radical surgery for locally advanced primary adenocarcinoma of anal fistula, and reviewed the recent treatment options and their outcomes in patients with primary adenocarcinoma of anal fistula. A 'new' diagnostic criteria for primary adenocarcinoma associated with anal fistula are proposed in the discussion. Algorithm for the diagnosis and management of primary adenocarcinoma associated with anal fistula is shown at the end of this paper.

Keywords: Anal fistula, Malignancy, Surgery, Review, Algorithm

J Med Assoc Thai 2019;102(8):939-44

Website: <http://www.jmatonline.com>

Received 8 Jun 2018 | Revised 27 Oct 2018 | Accepted 28 Oct 2018

Since anal fistula has been one of the most common diseases in coloproctology, with an estimated incidence of 1.2 to 2.8 per 10,000 population per year⁽¹⁾, malignant transformation, or primary adenocarcinoma of anal fistula is seldom documented. The relation between long-standing anal fistula and mucinous adenocarcinoma was first described by Rosser in 1934⁽²⁾. The cancer could develop in the fistula tract or in the scars after an operation for anal fistula or abscess. The presence of tuberculosis or other infections may obscure a co-existing cancer⁽³⁾. Malignant transformation in anal fistula is believed to occur as a result of chronic inflammation of anal fistula. The time interval between the onset of benign anal fistula and malignant change reported in the literature is various, but usually more than 5 to 10 years⁽⁴⁾. Patients having adenocarcinoma associated with anal fistula generally present with a long history of unhealed anal fistula, with or without mucous

discharge, or growth at the perianal skin or in the anal canal.

Tissue biopsy is the most effective methods for determining malignant transformation, but the deep tissue of anal fistula, not just only the external opening of the tract may be required. Owing to the rarity of this malignancy as well as the requirement of precise tissue sampling and a high index of suspicion, early diagnosis of adenocarcinoma associated with anal fistula is seldom reached and consequently, correct treatment is often delayed. Colonoscopy and cross-sectional imaging studies are helpful to distinguish primary adenocarcinoma arising in anal fistula from secondary adenocarcinoma due to the implantation of malignant cells from proximal colorectal cancer or the direct invasion of rectal cancer to perianal skin. The treatment of primary adenocarcinoma of anal fistula is not well defined, but most cases required abdominoperineal resection (APR). The authors report a case of locally-advanced mucinous adenocarcinoma arising in the deep portion of anal fistula treated successfully by en-bloc APR and distal sacrectomy.

Correspondence to:

Boonnithi W.

Colorectal Surgery Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Phone: +66-2-4198005

Email: bank_ashura@hotmail.com

Case Report

The patient was a 64-year-old man with well-controlled type II diabetes mellitus. He has had

How to cite this article: Boonnithi W, Lohsiriwat V. Primary Adenocarcinoma of Anal Fistula: A Case Report and Literature Review. J Med Assoc Thai 2019;102:939-44.

intermittent purulent discharge from an opening in the perianal region for seven years. He was diagnosed of a high transphincteric-type posterior anal fistula. At that time, a physical examination revealed no palpable mass in the anal canal except an indurated area at the posterior midline of anal canal indicating the internal opening of the fistula. There were two external openings yielding some purulent discharge located at right posterolateral aspect and posterior midline of perianal region about 10 cm from the anal verge. Magnetic resonance imaging (MRI) of the pelvis showed high transphincteric fistula with an internal opening at the posterior midline about 4 cm above the anal verge, with some inflammatory changes in the soft tissue surrounding the tract (Grade 3 in St. James' University Hospital classification).

He underwent a ligation of intersphincteric fistula tract (LIFT) with the partial excision of distal fistula tract and its external opening. Pathological examination of the specimen showed well to moderately-differentiated mucinous adenocarcinoma. Colonoscopy was performed and found no colorectal lesion. Computed tomography (CT) scan of chest and abdomen including the pelvis showed a hypodense lesion with rim and internal septate enhancement with focal internal calcification at the presacral region that had tract connected between the skin and anal canal. The lesion adhered to sacral bone with some bony destruction of the fifth sacral vertebra. No distant metastasis was found (Figure 1).

Three months after an index operation, the patient underwent en-bloc APR with S4-S5 sacrectomy and myocutaneous flap reconstruction (Figure 2). Post-operative recovery was uneventful. The patient had no change in walking ability and bladder control. Pathological examination of this specimen revealed low-grade mucinous adenocarcinoma arising in the distal part of posterior anal fistula and invading to the cortex and medulla of distal sacrum and surrounding soft tissue. All surgical margins were free and there was no nodal metastasis. After discussing with our multi-disciplinary team, the patient did not receive any adjuvant treatment. There was no sign of recurrence after two years of regular surveillance.

Discussion

The development of primary adenocarcinoma in cryptoglandular anal fistula is rare. It is considered as a different entity from malignant transformation of perianal fistula in Crohn's disease or secondary adenocarcinoma in anal fistula due to the implantation of malignant cells from proximal colorectal cancer.

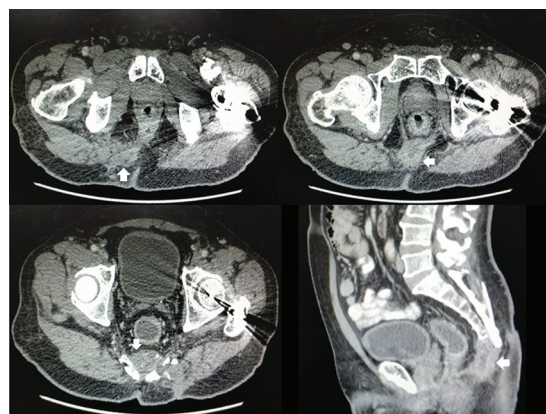


Figure 1. CT scan of abdomen and pelvis showed primary mucinous adenocarcinoma arising in a high transphincteric-type posterior anal fistula with an invasion to the distal part of sacrum (S5 level). White arrows indicated the location of adenocarcinoma-associated anal fistula.

The relationship between cryptoglandular anal fistula and primary adenocarcinoma of anal fistula is not fully understood but may be related to chronic infection and inflammation since primary adenocarcinoma arising in anal fistula is likely to be seen in a long-standing fistula. However, it is also possible that the cancer is de novo and presents as fistula.

Primary adenocarcinoma in cryptoglandular anal fistula need to be differential from the implantation of malignant cells from proximal colorectal cancer into a preexisting anal fistula (known as secondary adenocarcinoma in anal fistula) and the direct invasion of rectal cancer to perianal skin⁽⁵⁾. Colonoscopy and cross-sectional imaging studies are helpful to distinguish these conditions. The serum level of carcinoembryonic antigen (CEA) is within the normal range in many studies^(9,11,16,25). Immunohistochemical study of the tissue is also useful to identify the origin of adenocarcinoma as colorectal cancer in origin is usually expressed CDX-2 and cytokeratins (CK) 20 but negative for CK7⁽⁶⁾.

Based on an extensive review of recent literature, the authors suggested that the diagnostic criteria for primary adenocarcinoma associated with anal fistula should include 1) a history of long-standing anal fistula, not necessarily over 10 years but should be at least two years, 2) no concomitant proximal colorectal cancer, 3) if a presence of or a history of colorectal cancer is evident, immunohistochemistry must show different tumor biology between colorectal cancer and malignancy in the fistula, 4) any anorectal mass



Figure 2. Intraoperative findings and procedures for locally advanced primary mucinous adenocarcinoma associated with anal fistula (en bloc abdominoperineal resection with distal sacrectomy and myocutaneous flap reconstruction).

should be an extension from the fistula harboring the carcinoma, and 5) cancer cells exist along the anal fistula lining with or without invasion to the underlying stroma. These criteria are somehow different from those originally purposed by Rosser⁽²⁾ in 1934, that the fistula precede the carcinoma by at least ten years, that the internal opening of the fistula is in the anal canal and outside the tumor itself, and that the only tumor present in the rectum or anal canal should be a direct extension from the carcinoma in the fistula.

Practically, primary adenocarcinoma associated with ‘cryptoglandular’ anal fistula should be suspected in a long-standing fistula (especially with an onset more than five to ten years), unhealed fistula even undergoing proper management, fistula with abnormal growth within or at its opening, or fistula with bloody or mucus discharge. Biopsy, or sometimes partial fistulectomy or tissue curettage of the deep portion of anal fistula, is the most effective ways to discover malignant change. Multiple biopsies of all suspected lesions are advisable.

Once the diagnosis is made with proper staging, surgical resection (e.g. APR) with adequate margin

remains the gold standard treatment of non-metastatic lesion. The present study showed that radical surgery (en bloc APR with S4-S5 sacrectomy and myocutaneous flap reconstruction) is required for locally advanced adenocarcinoma arising in anal fistula. Extended tumor resection with free surgical margin can lead to a good oncological outcome. Local recurrence is more common than distant recurrence, and a positive resection margin was associated with increased local recurrence and decreased overall survival⁽⁷⁾. Although there is no consensus on adjuvant treatment in those with nodal metastasis or incomplete resection, many investigators have advocated that chemoradiation or chemotherapy alone should be considered in such cases⁽⁷⁾. Neoadjuvant chemoradiation may play a role in downsizing of locally advanced disease⁽⁸⁾. Chemotherapy regimen for colorectal cancer is usually applied to this malignancy. Table 1 summarizes the presentation, treatment, and outcomes of primary adenocarcinoma associated with ‘cryptoglandular’ anal fistula from studies published in the English literature between 2003 and 2017^(5,9-25).

According to a summary in Table 1, all (except

Table 1. Summary of primary adenocarcinoma associated with cryptoglandular anal fistula reported in the English literature from 2003 to 2017

First author, year	Country	n	Onset of fistula	Treatment	Outcomes
Erhan, 2003 ⁽⁹⁾	Turkey	1	15 years	APR	No recurrence at 3 years
Hisham, 2006 ⁽¹⁰⁾	Malaysia	1	2 years	RT	Not report
Sato, 2006 ⁽¹¹⁾	Japan	1	30 years	APR + CMT	No recurrence at 5 years
Ibanez, 2006 ⁽¹²⁾	Spain	1	30 years	NCRT + APR	Not report
Leal, 2007 ⁽¹³⁾	Brazil	1	18 years	APR	No recurrence at 1 years
Ong, 2007 ⁽¹⁴⁾	Singapore	4	30 years	APR	No recurrence at 1 years
			3 years	APR + CMT	No recurrence at 2 years
			30 years	APR	No recurrence at 3 years
			5 years	APR	No recurrence at 3 years
Okada, 2008 ⁽¹⁵⁾	Japan	1	Unclear	APR + CRT	No recurrence at 2 years
Yang, 2009 ⁽¹⁶⁾	China	3	15 years	RT	Tumor progression at 2 years
			3 years	CRT	Tumor progression at 2 years
			12 years	None	Metastasis & died at 2 years
Venclauskas, 2009 ⁽¹⁷⁾	Lithuania	1	15 years	APR	Not report
Diffaa, 2011 ⁽¹⁸⁾	Morocco	1	22 years	APR	No recurrence at 2 years
Ohta, 2013 ⁽¹⁹⁾	Japan	1	45 years	RT + APR	Died due to renal failure
Santos, 2014 ⁽²⁰⁾	Portugal	1	12 years	RT + APR	No recurrence at 3 years
Yamada, 2014 ⁽⁵⁾	Japan	5	3 years	APR	No recurrence at 3 years
			56 years	APR	No recurrence at 3 years
			25 years	APR	Recurrence & died at 5 years
			2 months	APR	No recurrence at 5 years
			2 months	APR	Recurrence & died at 2 years
Borpujari, 2015 ⁽²¹⁾	India	1	40 years	APR + CRT	Not report
Nazki, 2015 ⁽²²⁾	India	1	14 years	CRT	Not report
Ilbawi, 2015 ⁽²³⁾	USA	1	3 years	Wide excision + CRT	No recurrence at 2 years
Mukai, 2016 ⁽²⁴⁾	Brazil	1	12 years	APR	Recurrence & died at 6 months
Stosic, 2017 ⁽²⁵⁾	Serbia	1	30 years	Wide excision + CRT	Plan for APR
Lohsiriwat, 2018 (present study)	Thailand	1	7 years	APR + distal sacrectomy	No recurrence at 2 years

APR=abdominoperineal resection; CMT=chemotherapy; CRT=chemoradiation; n=number of patient; NCRT=neoadjuvant chemoradiation; RT=radiotherapy

two cases from Japan) patients with primary adenocarcinoma arising in anal fistula had an onset of fistula presentation at least two years, with the longest interval between onset and malignant change of 30 years. For eligible cases to surgery, all except two underwent APR with or without pre-operative (chemo) radiation. In the present report, distal sacrectomy was required for local invasion of the tumor. Although the disease-free survival (DFS) and overall survival (OS)

cannot be determined from this table, in a Japanese literature 5-year OS and DFS of patients with primary adenocarcinoma arising in anal fistula underwent either APR or wide local excision were 69% and 53%, respectively⁽⁷⁾.

In conclusion, primary adenocarcinoma associated with anal fistula is uncommon, but physician must be aware of this malignant change in long-standing fistula, unhealed fistula that even underwent proper

Suspicion	Clinical features of primary adenocarcinoma of anal fistula - Long-standing fistula - Unhealed fistula even undergoing proper management - Fistula with abnormal growth within or at its opening - Fistula containing bloody or mucus discharge
Diagnosis	Multiple biopsies (or tissue curettage) of all suspected lesions Colonoscopy - To rule out secondary adenocarcinoma (implantation of colorectal cancer to preexisting anal fistula) or locally advanced anorectal cancer causing anocutaneous fistula
Staging	CT scan of chest, abdomen and pelvis ± MRI of pelvis
Treatment	Localized CA: abdominoperineal resection, or wide excision Locally advanced CA: surgery ± (neo-)adjuvant (chemo-)radiation Metastatic CA: best supportive care, palliative (chemo-)radiation or palliative surgery

Figure 3. Algorithm for the diagnosis and management of primary adenocarcinoma associated with anal fistula.

management, fistula with abnormal growth within or at its opening, or fistula with bloody or mucus discharge. Biopsy is the most effective mean to discover malignant change. Surgery is the mainstay treatment and the applications of (neo)adjuvant treatment is depending on stage of the tumor and adequacy of surgical resection. Algorithm for the diagnosis and management of primary adenocarcinoma associated with anal fistula is shown in Figure 3.

What is already known on this topic?

Malignant transformation can occur in a long-standing anal fistula partly due to a result of chronic inflammation. Surgical resection with adequate margin is the gold standard treatment of non-metastatic adenocarcinoma associated with anal fistula.

What this study adds?

This paper reported a successful radical surgery for locally advanced primary adenocarcinoma of anal fistula. According to a comprehensive review of recent evidence, we purposed 'new' diagnostic criteria for primary adenocarcinoma associated with anal fistula and suggested an algorithm for the diagnosis and management of this condition.

Conflicts of interest

The authors declare no conflict of interest.

References

- Zanotti C, Martinez-Puente C, Pascual I, Pascual M, Herreros D, Garcia-Olmo D. An assessment of the incidence of fistula-in-ano in four countries of the European Union. *Int J Colorectal Dis* 2007;22:1459-62.
- Rosser C. The relation of fistula in ano to cancer of anal canal. *Trans Am Proctol Soc* 1934;35:65-71.
- Skir I. Mucinous carcinoma associated with fistulas of long-standing. *Am J Surg* 1948;75:285-9.
- Dukes CE, Galvin C. Colloid carcinoma arising within fistulae in the anorectal region. *Ann R Coll Surg Engl* 1956;18:246-61.
- Yamada K, Miyakura Y, Koinuma K, Horie H, Lefor AT, Yasuda Y, et al. Primary and secondary adenocarcinomas associated with anal fistulae. *Surg Today* 2014;44:888-96.
- Chu PG, Chung L, Weiss LM, Lau SK. Determining the site of origin of mucinous adenocarcinoma: an immunohistochemical study of 175 cases. *Am J Surg Pathol* 2011;35:1830-6.
- Sato T, Yamada K, Ogata S, Tsuji Y, Iwamoto K, Saiki Y, et al. Carcinoma associated with anal fistula: A clinicopathologic study of 25 patients. *Jpn J Gastroenterol Surg* 2016;49:579-87.
- Gaertner WB, Hagerman GF, Finne CO, Alavi K, Jessurun J, Rothenberger DA, et al. Fistula-associated anal adenocarcinoma: good results with aggressive therapy. *Dis Colon Rectum* 2008;51:1061-7.
- Erhan Y, Sakarya A, Aydede H, Demir A, Seyhan A, Atici E. A case of large mucinous adenocarcinoma arising in a long-standing fistula-in-ano. *Dig Surg* 2003;20:69-71.
- Hisham RB, Rahman SA, Gul YA. Mucinous adenocarcinoma arising from chronic perianal fistula. *Surg Pract* 2007;11:88-9.
- Sato H, Maeda K, Maruta M, Kuroda M, Nogaki M, Nogaki M. Mucinous adenocarcinoma associated with chronic anal fistula reconstructed by gracilis myocutaneous flaps. *Tech Coloproctol* 2006;10:249-52.
- Ibáñez Aguirre FJ, Erro Azcárate JM, Aranda Lozano F, Almendral López ML, Valentí Ponsa C, Echenique Elizondo M. Mucinous adenocarcinoma on chronic perianal fistula treated by neoadjuvant QT-RT neoadjuvante and laparoscopic abdomino-perineal resection. *Rev Esp Enferm Dig* 2006;98:310-2.
- Leal RF, Ayrizono ML, Coy CS, Fagundes JJ, Goes JR. Mucinous adenocarcinoma derived from chronic perianal fistulas: report of a case and review of the literature. *Tech Coloproctol* 2007;11:155-7.
- Ong J, Jit-Fong L, Ming-Hian K, Boon-Swee O, Kok-Sun H, Eu KW. Perianal mucinous adenocarcinoma arising from chronic anorectal fistulae: a review from a single institution. *Tech Coloproctol* 2007;11:34-8.
- Okada K, Shatari T, Sasaki T, Tamada T, Suwa T, Furuuchi T, et al. Is histopathological evidence really essential for making a surgical decision about mucinous carcinoma arising in a perianal fistula? Report of a case. *Surg Today* 2008;38:555-8.
- Yang BL, Shao WJ, Sun GD, Chen YQ, Huang JC. Perianal mucinous adenocarcinoma arising from chronic anorectal fistulae: a review from single institution. *Int J Colorectal Dis* 2009;24:1001-6.

17. Venclauskas L, Saladžinskas Z, Tamelis A, Pranys D, Pavalkis D. Mucinous adenocarcinoma arising in an anorectal fistula. *Medicina (Kaunas)* 2009;45:286-90.
18. Diffaa A, Samlani Z, Elbahlouli A, Rabbani K, Narjis Y, Elamansouri F, et al. Primary anal mucinous adenocarcinoma: a case series. *Arab J Gastroenterol* 2011;12:48-50.
19. Ohta R, Sekikawa K, Goto M, Narita K, Takahashi Y, Ikeda H, et al. A case of perianal mucinous adenocarcinoma arising from an anorectal fistula successfully resected after preoperative radiotherapy. *Case Rep Gastroenterol* 2013;7:219-23.
20. Santos MD, Nogueira C, Lopes C. Mucinous adenocarcinoma arising in chronic perianal fistula: good results with neoadjuvant chemoradiotherapy followed by surgery. *Case Rep Surg* 2014;2014:386150.
21. Borpujari PJ, Bhargava S. Unusual presentation of mucinous adenocarcinoma in a post fistulectomy case. *Med J Armed Forces India* 2015;71:S111-S113.
22. Nazki S, Chowdari NA, Parray FQ, Wani RA, Samad L. Adenocarcinoma arising from fistula in ano. *J Gastrointest Dig Syst* [Internet]. 2015 [cited 2018 Jan 17];5(6). Available from: <https://www.omicsonline.org/open-access/adenocarcinoma-arising-from-fistula-in-ano-2161-069X-1000370.php?aid=65956>.
23. Ilbawi AM, Simianu VV, Millie M, Soriano P. Wide local excision of perianal mucinous adenocarcinoma. *J Clin Oncol* 2015;33:e16-e18.
24. Mukai N, Pinheiro LV, Ayrizono ML, Barreiro GC, Kharmandayan P, Akinaga MH, et al. Mucinous adenocarcinoma associated with chronic suppurative hidradenitis: Report of a case and review of the literature. *Int J Surg Case Rep* 2016;26:12-6.
25. Stosic M, Mihajlovic S, Stojanovic I, Lalic M. Mucinous carcinoma of the anal canal arising from perianal fistula. *Hellen J Surg* 2017;89:32-6.