CASE REPORT

Adenocarcinoma Developing at the Level of a Chronic Perianal Fistula by Cell Implantation from a Proximal Rectal Cancer

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Abstract

Anorectal adenocarcinoma is a very rare complication which can occur during the long-lasting evolution of perianal fistulas (PAF), chronic inflammation being the main predisposing factor incriminated for malignant evolution. Moreover, in rare cases (only 28 being published until now), adenocarcinoma developing at the level of a perianal fistula may occur by migration of tumoral cells originating from a rectal cancer into the granulation tissue of the fistula. We present the case of a patient with a rectal adenocarcinoma that has metastasized to a perianal fistula, in evolution for 7 years. Clinical suspicion of malignant seeding at the site of the fistula has been confirmed by immunohistochemical studies.

Keywords: perianal fistula, rectal cancer, metastasis.

Rezumat

Adenocarcinomul anorectal este o complicație foarte rară ce poate surveni în cursul evoluției de lungă durată a fistulelor perianale, inflamația cronică fiind principalul factor predispozant pentru malignizare. Pe de altă parte, în cazuri rare (doar 28 fiind publicate până acum), adenocarcinomul dezvoltat la nivelul unei fistule perianale poate surveni prin migrarea de celule tumorale de la nivelul unui cancer rectal la țesutul de granulație al fistulei. Prezentăm cazul unui pacient cu adenocarcinom rectal care a metastazat la nivelul unei fistule perianale în evoluție de 7 ani. Suspiciunea clinică de malignitate la nivelul fistulei a fost confirmată de analiza imunohistochimică.

Cuvinte cheie: fistulă perianală, cancer rectal, metastază.

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INTRODUCTION

Adenocarcinoma diagnosed at the level of a perianal fistula is a very rare lesion. It may occur either by local malignant complication of long-lasting perianal fistulas or by seeding of tumoral cells from a synchronous colo-rectal carcinoma.

In the first instance, chronic inflammation is incriminated as being the main predisposing factor for malignancy[1]. The time required for a perianal fistula to reach malignant transformation is about 10 years[2]. The diagnosis is frequently delayed due to the modified local aspect caused by the chronic evolution of the fistula. The pattern of malignant tumoral invasion is usually infiltrative, the tumor often developing inside the fistula. Because of this, biopsy is difficult to perform and frequently shows false negative results for malignancy[3]. Therefore, in case of suspected malignant transformation of a chronic perianal fistula, multiple biopsies are mandatory in order to obtain a conclusive histological diagnosis.

Specific workup should exclude the second possibility – an adenocarcinoma developed on a perianal fistula by neoplastic cell seeding from a colorectal cancer to the granulation tissue of the fistula[4]. Therefore, colonoscopy is required in all cases of cancers developed in this region and pelvic MRI is useful for preoperative staging. Radio- and chemotherapy have an important role in the management of these tumors (both as neoadjuvant treatment in resectable tumors or as a definitive treatment in poor surgical candidates)[1]. Abdominoperineal resection is the preferred surgical treatment.

CASE PRESENTATION

A 53-year-old patient was diagnosed in 2005 with a perianal fistula for which, in an other hospital, he underwent two surgical interventions consisting of fistulectomy, both followed by recurrence of the fistula. He was admitted in our clinic in October 2012 with two posterior perianal fistulas; the rectal examination found a tumor of about 3cm, above the dentate line, on the posterior wall of the inferior rectum. The anuscopic examination also revealed the internal orifice of the fistula, situated at the level of the dentate line, at "nine o'clock" in left lateral decubitus and stage III hemorrhoids. The patient's blood tests were within normal range (no anemia, no inflammatory syndrome, normal levels of the digestive tract tumoral markers CEA and CA 19-9). Total colonoscopy revealed an ulcerated tumour of about 3cm in the vicinity of the dentate line, from which 6 biopsies were collected (notable stiffness of the tumor during biopsy was remarked). Since the initial histological results of the rectal tumor showed only ulceration with areas of mucus secretion including isolated „signet ring" cells, with suspected atypia, but without any infiltrative-tumoral aspects, new biopsies were collected from the rectal exophytic tumor. The histological examination was again inconclusive, showing non-specific mucosal ulceration without infiltrative-tumoral aspects. Due to these inconclusive results and to the fact that the primary symptoms of the patient were due to the suspect perianal fistula, fistulectomy was performed. The removed fistulous tract, which had a pseudotumoral aspect, was sent for his-

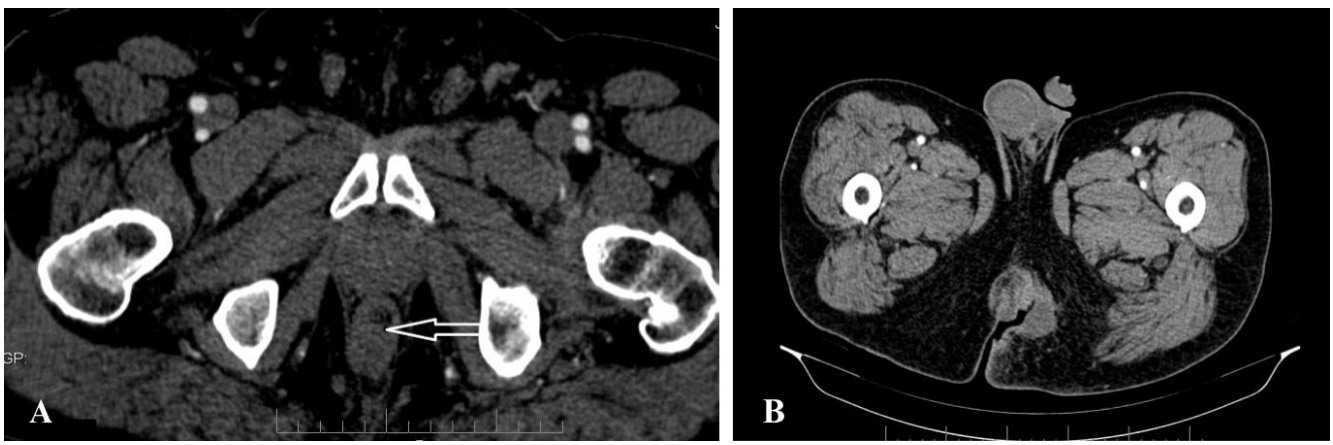

Figure 1. Abdominal-pelvic CT scan performed following fistulectomy: a) thickening of the posterior rectal wall – initially interpreted as inflammatory; b) fluid perianal collection with cutaneous communication (corresponding to the post resection wound following excision of the fistulous tract).

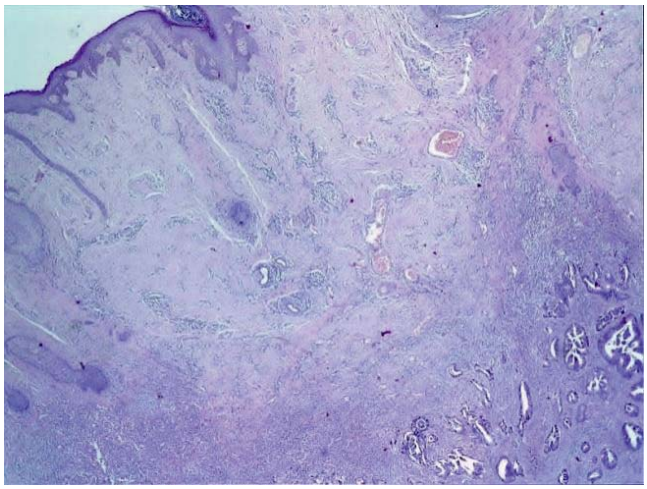

Figure 2. Fistula specimen HE, 100x; Tissue fragment with squamous keratinized epithelium and malignant glandular structures with stromal infiltration.

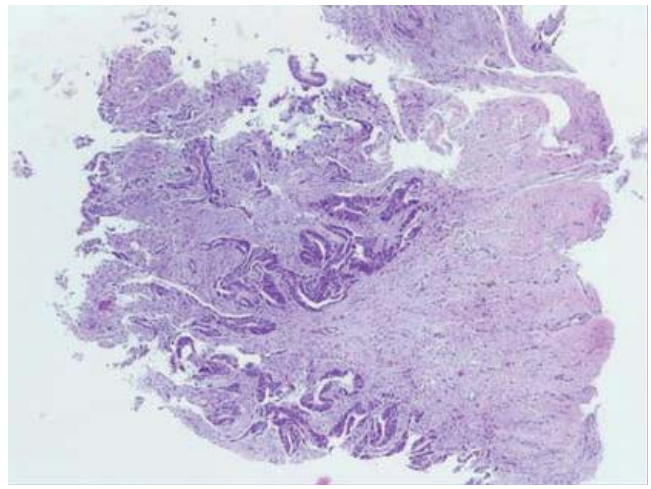

Figure 3. Rectal tumor biopsy HE, 50x; biopsic fragment from ulcerated rectal mucosa, with proliferation of ulcerated, moderately differentiated, tubular adenocarcinoma, with positive desmoplastic reaction.

tological examination. In the meantime, workup was completed by a thoracic-abdominal-pelvic CT scan (Figure 1), which described a 14cm-long fluid perianal collection with cutaneous communication (corresponding with the post resection wound after the excision of the fistulous tract) and a thickening of the posterior wall of the inferior rectum.

Histological examination of the resected fistulous tract showed fibrous-hyaline and adipose tissue with focal inflammatory infiltration, rare „signet ring" cells and infiltrative atypical glandular structures; the final histological diagnosis was mucinous (colloid) adenocarcinoma infiltrating the fibrous-connective tissue (Figure 2).

The patient underwent a specific treatment protocol for lower rectal cancer: a laparoscopic colostomy was performed in October 2012, prior to initiating radiotherapy, followed by neoadjuvant radio-chemotherapy. In January 2013 an abdominoperineal resection was performed, with uncomplicated postoperative course. The resected specimen was sent to histological examination, presenting at 3cm above the anal verge an indurated area, with superficial ulceration (diameter of 4cm), with histological aspect of G1-G2 well-moderately differentiated tubulo-papillary adenocarcinoma, extracellular mucin hypersecretion, with invasion throughout the entire wall of the rectum (pT3). The tumor cells from the fistula specimen had a similar aspect with those from the rectal tumor (Figure 3).

The resection margins were tumor free and the 12 examined lymph nodes (with diameters between 0.3 and 0.8cm) showed no metastases (pN0). Immunohistochemical examination of the two tumors has shown similar aspects: both tumors were CK20 (Figure 4), CK7 (Figure 6) and CDX2 (Figure 5) positive, suggesting the rectal origin of the tumoral cells that have migrated at the level of the perianal fistula, thus differentiating it from a locally developed malignancy. In order to exclude direct invasion or metastasis to adjacent organs, CK5/6 (Figure 7) was determined in the metastatic lesion, which showed a negative reaction.

The final diagnosis was inferior rectal cancer metastasized to a perianal fistula.

Considering the final staging of the tumor, pT3N0M0, G1-G2, with neoadjuvant radio and chemotherapy, followed by radical surgical resection, it was decided that there was no need for adjuvant chemotherapy. The patient was followed-up according to the rectal cancer postoperative surveillance protocols, with a favorable outcome - no sign of recurrence at 7 years following radical surgery.

DISCUSSION

1. Adenocarcinoma occurring locally at the level of a chronic PAF:

Most of the adenocarcinomas occurring at the level of a chronic PAF develop as a rare local complication. A primary neoplasm at the site of a perianal fistula is diagnosed with a frequency of 0,1% of all cases of perianal fistula[5,6]. There are few reports that address this subject. The first scientific paper mentioning malig-

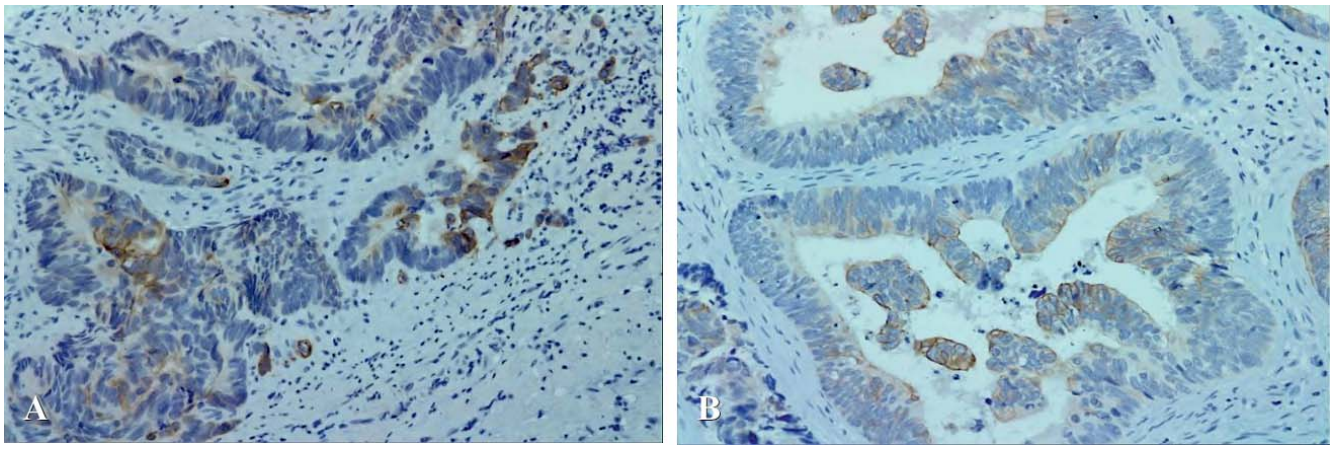

Figure 4. CK20 positivity in a) the rectal tumor (moderately differentiated tubular adenocarcinoma with desmoplastic reaction) and b) in the fistula (tubular adenocarcinoma).

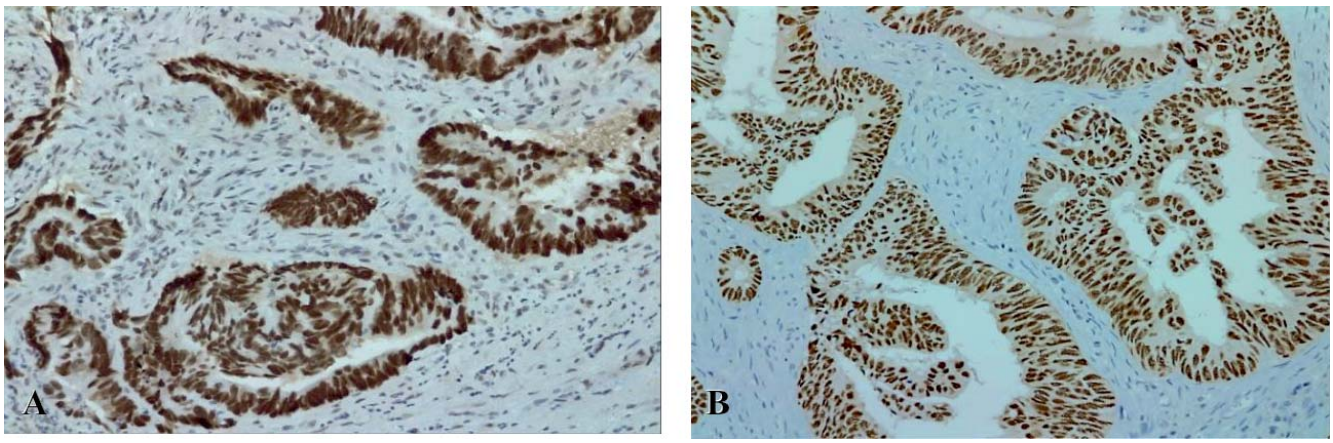

Figure 5. Tumoral cells showing a positive nuclear reaction for CDX2 in a) the rectal mucosa (tubular adenocarcinoma) and in b) the tumoral cells of the perianal fistula.

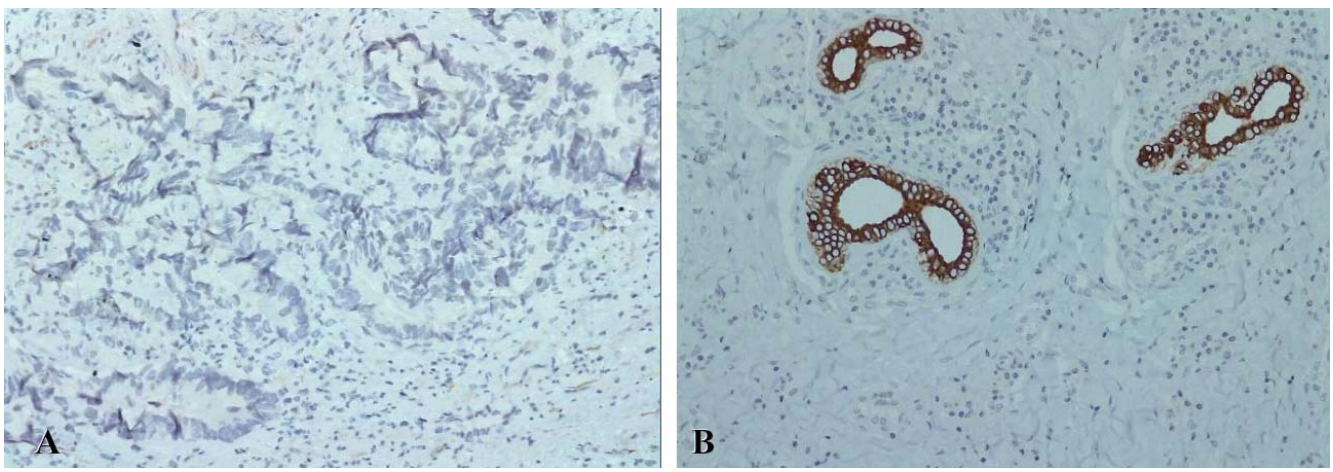

Figure 6. Positive CK7 reaction in a) rectal mucosa with in isolated tumoral cells and b) fragment from the perianal fistula (intense CK7 positive reaction in typical anal glands, in the submucosa).

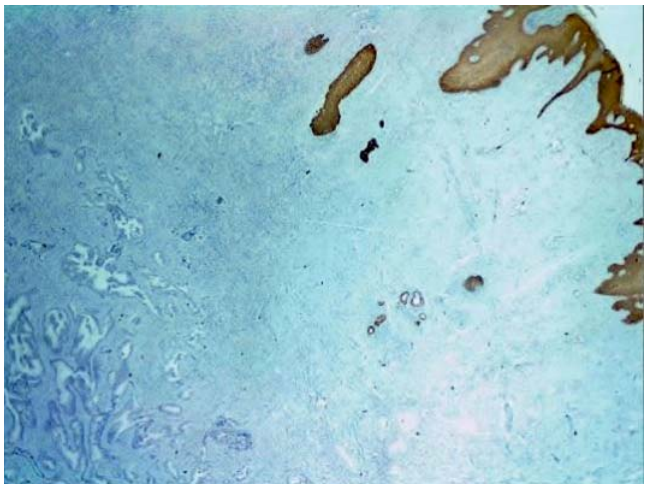

Figure 7. CK5/6 negative reaction in the fistular tumor cells (lower left) and positivity in control squamous epithelium.

nancy in perianal fistulas dates to 1934, when Rossier published a series of 6 cases of chronic perianal fistulas, on which anal malignancies have developed[7]. At the time being, he established the following diagnosis criteria: long evolution of the fistula, the absence of an anorectal tumor and the internal orifice of the fistula emerging in healthy tissue, unaffected by a tumor. Subsequently, Skir and Mcintyre have added another diagnostic element - the induration of the fistula, with exacerbated perianal pain and mucus secretion[8,9].

Presently, the mechanism by which malignancy is developed on perianal fistula is not completely clarified. Throughout the years, many hypotheses have been proposed based on clinical and paraclinical observations:

- The first supposition belongs to Dukes and Galvin, who suggested that the abnormal congenital duplication of the intestinal tract would be the starting point to developing anorectal cancer[10].
- Some authors have concluded that the origin of the extramucosal anal tumors, including the ones developed on perianal fistulas, is in the anal glands[11,12].
- In 1981, Getz et al. considered that, in perianal fistulas, a focal adenomatous hyperplasia of the anal glands occurs, which can further progress into a well differentiated anorectal adenocarcinoma[13].
- Another theory suggests that the origin of anorectal cancers developed in perianal fistulas is from rectal mucosal cells migrated within the anal canal – proven by the positive acetyl sialic acid coloring of the tumoral cells[14].

2. Adenocarcinoma developed at the level of a PAF by cell seeding from a proximal rectal cancer:

Seeding of the tumoral cells that have detached and migrated from the site of the primary tumor to a perianal fistula is by far the rarest possibility. Most rectal tumors metastasize through lymphatic, hematogenous or peritoneal ways, or by local extension to adjacent organs. Metastasizing from a rectal cancer to the anal canal in patients without perianal fistulas is also possible, as reported by Nishikawa et al.[15] - a patient with rectal cancer and multiple liver and lymph node metastases also had an anal metastasis. Implantation of tumoral cells from a rectal cancer into different abdominal structures, including the distal ano-rectal mucosa is also possible, following different surgical procedures or other maneuvers that may affect the mucosa. There are rare reported cases of implantation of colorectal tumoral cells in perianal postoperative wounds at the site of stapler insertion[16], post haemorrhoidectomy[17], after colonoscopic biopsy[18], or at the site of a retractor used for a colo-anal anastomosis[19].

Metastasizing of a rectal tumor to a perianal fistula is rarely described, only 28 cases being cited to this day: the first case belongs to Guiss et al., in 1954[20] and the most recent was published by Takahashi et al. in 2015[6]. The diagnosis of this condition is difficult, in many cases being only possible after histopathological examination of the resected fistula. Some clinical facts may suggest this condition, like recent occurring changes in the evolution of a chronic perianal fistula, such as increased purulent discharge, a modified aspect of the discharge (which becomes hemorrhagic), increased pain or local induration. These signs should raise the suspicion of malignancy, either primary or secondary, at the site of a perianal fistula.

In order to minimize this risk of a missed diagnosis, it is recommended that surgical procedures on a PAF be preceded by colonoscopy, even in the absence of specific symptoms for colorectal cancer. The same approach should precede a fistulectomy procedure, and the resected specimen should be sent to histological examination regardless of the macroscopic aspect. Also, when cancer developed on a perianal fistula is diagnosed, colonoscopy is required in order to exclude seeding of tumoral cells from above.

Only histological examination may differentiate between a metastasis from a colorectal cancer at the fistula site and a primary tumor developed in the fistula. In case of metastatic seeding into the PAF, immunohistochemical examination of the specimens reveals

the similarity between the tumoral cells implanted in the perianal fistula and those of the primary tumor. The distinction between the two is settled by immunohistochemical analysis of CK20 and CK7. In the case of a PAF adenocarcinoma developed by implantation from a proximal tumor, there is Ck20 positivity (96%) and CK 7 negativity (in over 80% of cases)[21]. In contrast, primary tumors developed in perianal fistulas are mostly CK 20 negative and CK 7 positive[22]. In this case report, the direct metastasis from the colorectal cancer was proven by the positive CK20 marker. As for CK7, the results may belong to the rare positive cases (20%).

The therapeutic approach is not clearly defined in these patients: some surgeons prefer a radical surgery (abdominoperineal resection), while others opt for a sphincter-preservation procedure. In our case, fistulectomy was performed due to the worsening local symptoms of the patient. This led to the diagnosis of malignancy at the level of the fistula, with subsequent diagnosis of the rectal tumor. Colorectal cancer treatment protocols were applied, with colostomy prior to chemo-radiotherapy, followed by an abdomino-perineal procedure.

CONCLUSIONS

Adenocarcinoma at the level of a chronic PAF may either develop locally or by seeding of tumor cells from a proximally situated cancer. Colonoscopy should be performed in all patients with chronic PAF and suspected or diagnosed malignisation, in order to exclude a simultaneous tumor. Immunohistochemical examination differentiate between the two conditions, implantation from a proximal tumor being more probable if there is Ck20 positivity and CK 7 negativity.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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