Rare and Aggressive Fistula-Related Cancer in Patients with Long Standing Fistulising Perianal Crohn’s Disease: Report of 3 New Cases and Short Review Of Literature

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Received Date: July 03, 2017, Accepted Date: July 31, 2017, Published Date: August 04, 2017.

Keywords: Crohn’s disease; Perianal fistulas; Cancer

Abstract
Malignant transformation of chronic perianal fistulas is considered as a rare and separate entity from the risk of colonic adenocarcinomas in patients with Crohn’s disease. Less than a hundred cases have been published in the past 60 years. Such diagnosis is difficult due to lack of symptoms specificity resulting in diagnosis delay and dramatic outcomes. We present three new cases of young patients with rare histological type and aggressive fistula-related cancer: respectively a high-grade neuroendocrine carcinoma poorly differentiated, a mucinous adenocarcinoma with colloid part and a metastatic squamous cell carcinoma. These patients had long standing Crohn’s disease. Their cancer was diagnosed at advanced stage and two of them died in less than six months. We discuss the modalities of surveillance of perianal Crohn’s disease and propose new attitude for screening these patients including regular MRI.

Introduction
The association between colorectal adenocarcinomas and inflammatory bowel diseases (IBD) has been well described for many years and has led to guidelines for cancer surveillance [1]. Even if the colorectal cancer risk is more present for ulcerative colitis, the excess of colorectal cancer risk for CD patients has been estimated at 1.9 and at 27.1 for small bowel cancer [2]. However, the risk of perianal fistula-related cancer in CD patients is less known and almost 30% of CD patients will develop perianal fistulas [3]. According to a meta-analysis of 20 clinical studies comprising a total of 40547 patients with CD-associated cancer, the incidence of fistula-related cancer was 0.2/1000 patient-years [4]. Only a few cases of fistula-related cancers have been described in the literature and most of them were adenocarcinomas and squamous cell carcinoma type [5]. Here, we report three new cases of patients that developed infrequent and aggressive tumors arising from perianal fistulas.

Case reports

Patient 1
The first patient was a 51 years-old man suffering from CD for 28 years, with small bowel, colonic and anorectal involvement. He first received salazopyrine and steroids. In 2011, he had perianal fistula with abscesses successfully managed by surgical incision following by setons placement associated with antibiotics. After sepsis control, infliximab therapy was begun.

In January 2014, he consulted for general condition deterioration associated with fever and perianal pain. A CT scan showed a large left rectal abscess and bilateral inguinal lymph nodes (Figure 1). The abscess was treated surgically with antibiotics therapy. Histopathological analysis of surgical biopsy discovered high-grade neuroendocrine carcinoma poorly differentiated, grade 3 with Ki-67 at 25%. PET scan didn’t show metastasis. After a protective colostomy, chemotherapy was started but prematurely stopped due to the uncontrolled perianal septic condition. He died a few days later.

Patient 2
The second patient is a 33 years-old man with luminal colonic and perianal CD for 25 years. He first received corticosteroid, then methotrexate and azathioprine. At 18 years-old, he presented with occlusive syndrome due to colonic stricture treated by left colectomy, followed by anti-TNF therapy. Infliximab had to be stopped due to severe allergic reaction and switched to adalimumab. At 28 years-old, the patient developed severe perianal disease with complex fistulas and abscesses treated by antibiotics and surgical management with discharge ileostomy. Infliximab was then successfully reintroduced.

In June 2014, the patient developed perianal painful mass associated with suppuration of recurrent fistulas. First macro biopsies were negative and he received vedolizumab therapy without any improvement of the symptoms. MRI showed a 10 cm diameter heterogeneous mass located in the gluteal region with extension towards the anal canal (Figure 2 and 3). Surgical biopsy was carried out under general anesthesia and pathological examination concluded to mucinous adenocarcinoma with colloid...
received azathioprine, then infliximab and finally adalimumab. It permitted disease stabilization and allowed the patient to have her first baby in 2012. Then during her second pregnancy, at 7 months, she consulted in an emergency for acute abdominal pain with obstructive syndrome due to sigmoid perforation. She underwent caesarean in an emergency with left colectomy with colostomy and Hartmann’s pouch. Two months later, colonoscopy found voluminous inflammatory anal tags, anal stenosis, and moderate colitis. Adalimumab was reintroduced. Histopathology of anal tags and macrobiopsy concluded to viral lesion without dysplasia but with the implication of oncogenic HPV.

In September 2015, she consulted for proctalgia relapse and rectal bleeding. The examination found aggravation of anal stricture. MRI showed voluminous pararectal mass (90 × 50 × 50 mm) with lymph nodes infiltration. Pathological examination of surgical biopsy concluded to invasive squamous cell carcinoma. PET-scan found bone metastasis. After multidisciplinary discussion, it was decided to treat her with radio-chemotherapy but with mediocre tolerance. Her general condition got progressively worse and she died only 6 months after diagnosis.

Discussion

Cancer degeneration of perianal fistula tract is described in the literature as a rare entity (less than a hundred published cases in 60 years). We reported here a series of three cases diagnosed in our center in only two years (between January 2014 and February 2016).

In our series, the mean duration of CD was twenty-seven years before the onset of cancer. Persistent chronic fistulas in long-standing CD, especially in young women, have been identified as potential risk factors for malignant transformation of fistulas [1]. Indeed, according to a systematic review of published case series and reports [5], 61% females involved. At cancer diagnosis, women were significantly younger than men (47 vs 53 years, p < 0.032). Prior to detection of cancer, the average duration of CD was 20 years and the average duration of fistula was 11.5 years (8.3 years for females). Most of tumors were adenocarcinomas (59%, n = 36) or squamous-cell carcinomas (31%, n = 19), and involved fistulas usually originated in rectum (59%, n = 36) [5].

In our series, two patients presented rare histological tumors: a high-grade neuroendocrine carcinoma poorly differentiated and a mucinous adenocarcinoma with colloid part respectively. The published data describe only one case of adenocarcinoid tumor rising in fistula tract in CD [6] and six cases of mucinous carcinoma [7]. In general population, mucinous carcinoma is rare with an overall incidence ranging from 7% to 18%, more frequently localized in the right-side colon, and tends to be associated with inflammatory process [8].

The third patient was diagnosed with a particularly aggressive squamous cell carcinoma with bone metastasis. In this last case, it’s interesting to note the positivity of HPV oncogenic virus in anal lesions. A recent retrospective study found that anal squamous neoplastic lesions in IBD were associated with HPV infection [9].

Tumour diagnosis process in fistulising CD usually needs several months to be achieved. In our cases, patients didn’t show up with specific symptoms, but with the refractory perianal disease. In a systematic review of 23 reports on fistula-related cancer, the average delay of cancer diagnosis was 11 months [7]. Moreover, in our cases, the first macrobiopsies performed on two of our patients, a few months before definitive diagnosis, were mistakenly reassuring. Only MRI performed in front of refractory perianal disease showed voluminous mass.
In conclusion, fistula malignant transformation in perianal CD is not exceptional and needs an active surveillance. In patients with long-standing perianal CD, a change in symptoms should always raise the suspicion of cancer [10]. Clinic and endoscopic examinations remain insufficient because of lack of symptoms and signs specificity resulting in diagnosis delay with poor prognosis. Optimum frequency and modalities of surveillance are not known. According to ECCO guidelines, surveillance should include a routine biopsy of any suspicious lesion and a biopsy under anesthesia or curettage of fistula tracts when needed [1]. However, we also think that regular MRI should be performed on all patients with the long-standing active perianal disease. Prospective studies to evaluate best frequency and impact on regular MRI for perianal Crohn’s disease surveillance are needed. Screening of patients for anal HPV could also be considered.

References


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Received Date: July 03, 2017, Accepted Date: July 31, 2017, Published Date: August 04, 2017.

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