Case history:

A 49 year-old female presented with a 5 year history of chronic anal fissure. The patient's past medical history is otherwise unremarkable. On digital rectal examination there was a very firm area in the right lateral position. Colonoscopy did not reveal any additional findings. A biopsy of the lesion was obtained and representative sections are shown below.

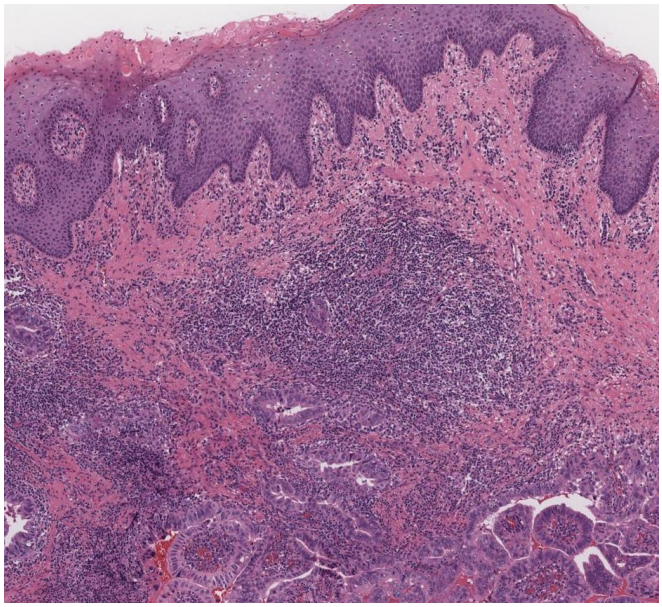

Figure 1. H&E, 5x.

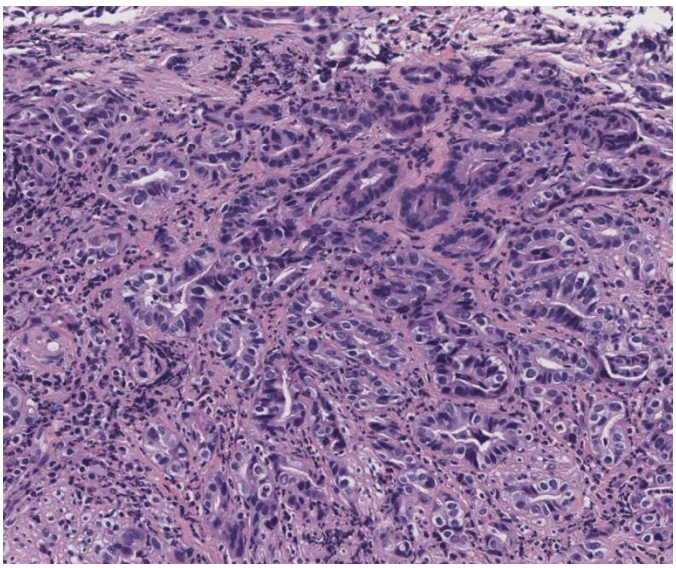

Figure 2. H&E, 20x.

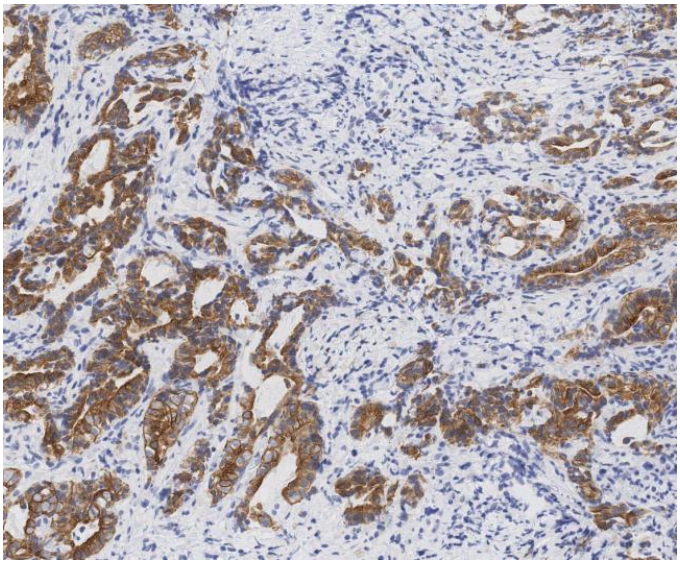

Figure 3. CK7, 5x.

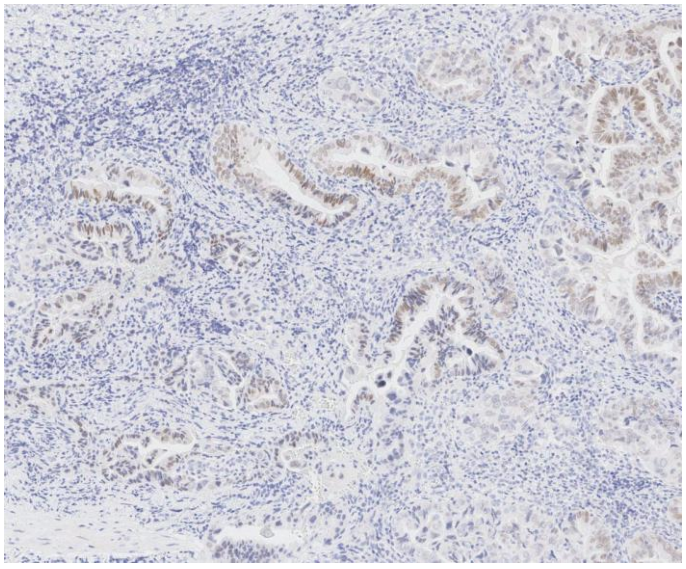

Figure 4. CDX-2, 20x.

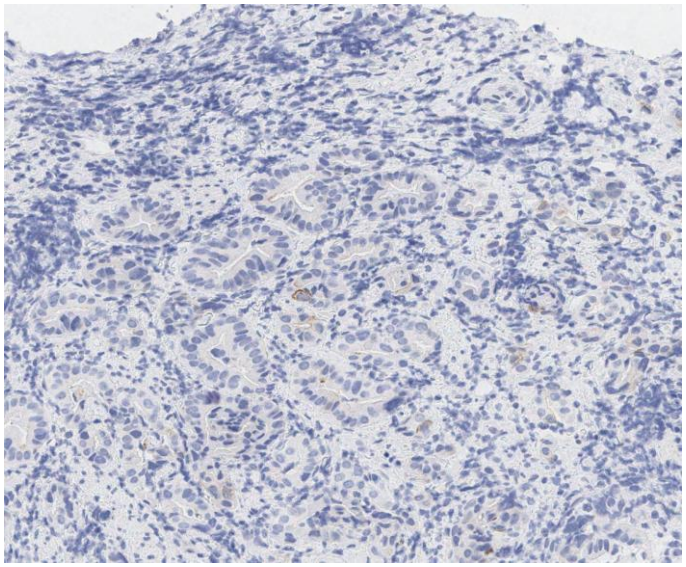

Figure 5. CK20 H&E, 20x.

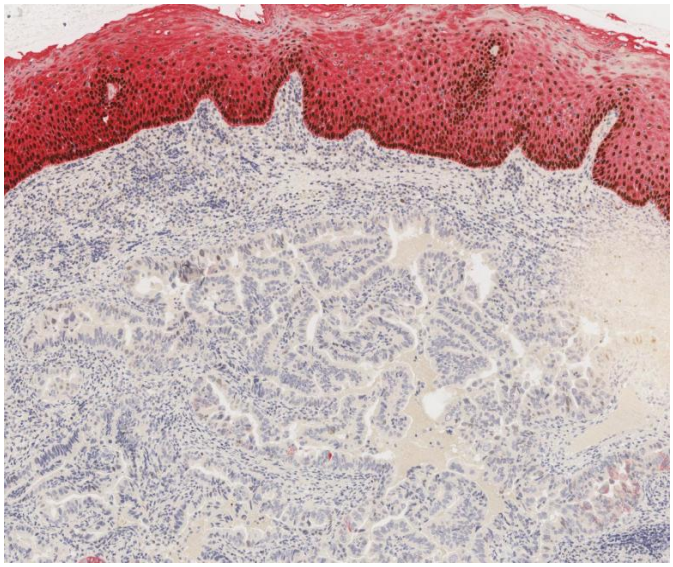

Figure 6. CK5 (red) and p63 (brown), 5x.

What is the correct diagnosis?

A. Colorectal adenocarcinoma
B. Anal gland carcinoma
C. Paget disease
D. Fistula associated adenocarcinoma

SCROLL DOWN TO NEXT PAGE FOR ANSWER AND DISCUSSION...

Answer and discussion:

B. Anal gland carcinoma

Sections show non-mucus producing neoplastic glands infiltrating submucosa of the anal canal. The glands themselves are composed of cuboidal epithelium with scan intercellular mucin. Squamous epithelium appears to be normal. By immunohistochemistry the neoplastic cells are strongly positive for CK7. CDX-2 demonstrates weak patchy nuclear staining. CK20 highlights rare single cells. Dual CK5 and p63 immunohistochemical stain is negative.

Anal gland carcinoma is a rare subtype of anal adenocarcinoma characterized by proliferation of small anal type glands with depleted mucin, which invade the wall of the anorectal area without an intraluminal component. It is thought to originate in the epithelium of the anal glands or ducts and historically, a continuity of the tumor with the normal glands was required for definite diagnosis [1,2]. Due to sampling issues or the possibility of tumor tracking down anal glands without originating from them, a descriptive morphologic definition of small anal type glands is preferred for the diagnosis [3]. The presenting symptoms include anal pain, bleeding and anal or perianal mass [4]. Association with fistula tracts can be seen in about 50% of cases [4]. The overall prognosis is poorer than for squamous cell carcinoma, with reported survival rates as low as 5% [4].

The main differential diagnosis of anal gland carcinoma is anal involvement from a colorectal carcinoma, a more common entity than primary anal carcinomas. According to WHO 2010 fourth edition [5], adenocarcinomas of the anal canal include adenocarcinomas arising in the anal mucosa, with a colorectal phenotype, and extramucosal carcinomas, which include adenocarcinomas of anal gland and fistula associated adenocarcinomas.

Attempts at identifying the immunohistochemical profile of anal gland carcinomas have indicated that they retain CK7+ expression similar to normal anal epithelium [6]. In contrast to colorectal carcinomas which are CK7-/CK20+, anal gland carcinomas are CK7+/CK20- [2,3,6,7] , with one case reported as CK7+/CK20+ [3]. Additionally, anal gland carcinomas also show loss of CK5/6 and p63 expression that is normally found in basal cell layer of normal anal epithelium [2,6].

In our case, given the morphological appearance of the anal tumor and the immunohistochemical profile of neoplastic cells that are strongly positive for CK7, focally positive for CDX2 and CK20, and negative for CK5 and p63, the tumor is best classified as an anal gland carcinoma.

(Answer A) Colorectal carcinoma with anal involvement is the main differential diagnosis of anal gland adenocarcinoma. The clinical history is positive for a colorectal lesion that extends to involve the anus. The neoplastic epithelium shows colorectal differentiation, with immunohistochemical profile that is CK7- and strong CK20+ and CDX2+. Our case had no colorectal lesion, and the anal lesion showed typical morphology of anal gland carcinoma with mucin depleted glands. The immunohistochemical profile of our case is also in keeping with

anal gland carcinoma, with strong CK7+, loss of CK5 and p63, and only focal CK20+ and CDX2+ cells.

(Answer C) Extramammary Paget disease (EMPD) is characterized by the presence of large malignant appearing cells with pale, granular, or vacuolated cytoplasm infiltrating the epidermis. In some instances, Paget cells can also have signet ring cell morphology. Although the vulva is the most common location for EMPD, the anal canal is among the other noted anogenital sites. Similar to that seen in other extramammary sites, Paget disease of the anal canal can be divided into two entities: true Paget disease, thought to originate from adnexal stem cells, (primary) and pagetoid extension of an associated synchronous or metachronous malignancy (secondary) [4,8]. Therefore pagetoid invasion of the surface epithelium may be seen in anal gland carcinoma (secondary Paget). The image provided below highlights a case of pagetoid extension of an underlying anal gland carcinoma into non-neoplastic squamous epithelium. If the internal malignancy is not sampled immunohistochemical staining can assist in delineating Pagetoid extension from true Paget disease cells.

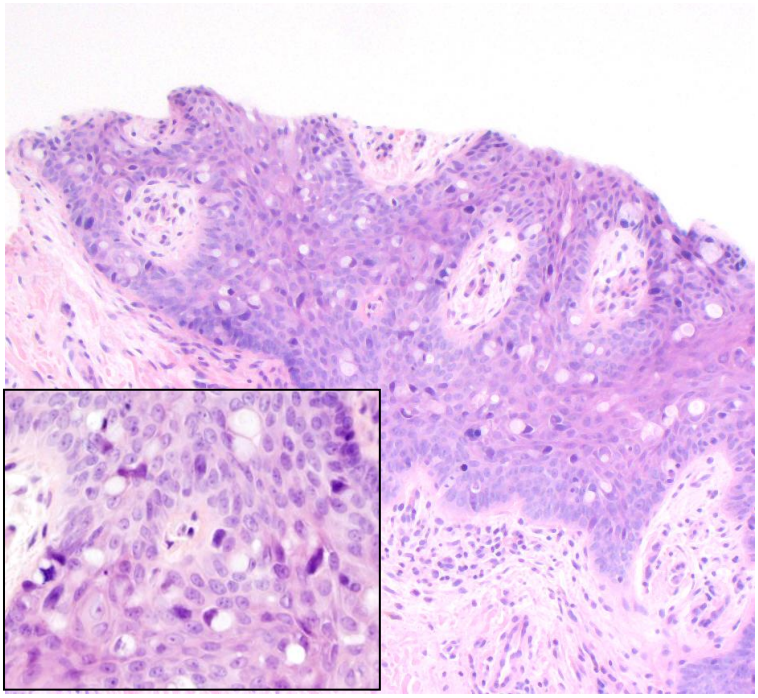

Figure 8 H&E, 10x and insert 40x.

Both are CK7+/CK20-, however, gross cystic disease fluid protein-15 (GCDFP-15) is positive in true Paget disease cells (GCDFP-15 positive)[5,8,9,10]. The immunohistochemical profile of the cells in the image provided above were as follows: CK7(+), CK20(-), GCDFP-15(-). Additional sampling also revealed an underlying carcinoma.

(Answer D) Fistula associated adenocarcinoma is an entity that links the presence of adenocarcinoma to chronic inflammation associated with fistula formation, either in the context of Crohn's disease [11] or as separate entity [12]. As mentioned, anal gland carcinomas can be associated with fistula formation[4], but that seems an incidental finding, rather than a cause-effect relationship. Moreover, the fistula associated adenocarcinoma is a mucinous adenocarcinoma that by immunohistochemistry shows colorectal rather than anal differentiation, in the form of a CK7-/CK20+/CDX2+ phenotype [11]. Our case did not have an associated fistula from the clinical history and it lacks the mucinous morphology and the appropriate immunohistochemical phenotype, thus making this diagnosis unlikely.

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Case contributed by:

Aurelia Busca, MD, PhD (Anatomical Pathology resident)

Sergey Pyatibrat, MD (GI staff pathologist)

University of Ottawa

Department of Pathology and Laboratory Medicine

Ryan Coates, MD (Anatomical and Clinical Pathology resident)

University of Vermont Medical Center

Department of Pathology and Laboratory medicine