CASE REPORT

Paget's disease of the anus masking a mixed adenoneuroendocrine tumour of the rectum

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SUMMARY

A man aged 83 years with vague perirectal symptoms had a delayed diagnosis of Paget's disease of the anus. A lack of thorough digital rectal examination failed to diagnose a mixed adenoneuroendocrine tumour of the rectum in a timely matter.

BACKGROUND

Paget's disease of the anus is a rare condition, and can be associated with an underlying adenocarcinoma. In our case, there was a missed opportunity to diagnose an underlying malignancy because of a lack of a digital rectal examination on behalf of the family practitioner. In addition to serving as an important reminder to perform thorough physical examinations, this case describes a rare occurrence of mixed adenoneuroendocrine carcinoma (MANEC) of the rectum.

CASE PRESENTATION

A Caucasian man aged 83 years with a medical history significant for hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease with stents and an implanted defibrillator, and lower GI bleed presented to his general practitioner for the symptom of occasional anal pruritus and scant bloody spotting with bowel movements without any rectal pain or frank blood per rectum. On examination, he was found to have a firm, erythematous, maculopapular perianal lesion and was referred to a dermatologist for further evaluation. He was prescribed an antifungal and various other topical medications, but these failed to relieve his symptoms. After 7 months of treatment, he was referred to a colorectal surgeon. On presentation, he was found to have a large ulcerated rash in the perianal area with thickened skin as well as a hard mass in his distal anal canal palpated on physical examination (figure 1).

INVESTIGATIONS

He was scheduled for examination under anaesthesia with sigmoidoscopy. This revealed a ~6 cm hard, ulcerated nodular mass on the left side of the anal canal extending proximally beyond the dentate line. Multiple biopsies were taken of the anal canal mass and perianal rash. Histopathology demonstrated nests, trabecula and single tumour cells infiltrating the subcutis, anal lamina propria and as pagetoid spread in the squamous mucosa. Two populations of tumour cells were identified. The adenocarcinoma component is composed of nests of cells with moderate amount of vacuolated

amphophilic cytoplasm and mild to moderate nuclear pleomorphism in mucin pools. Rare cells showed signet cell morphology (figure 2A, B). Intraepithelial pagetoid spread in the anal mucosa is focally noted. The neuroendocrine component is composed of nests, ribbons and single cells with granular amphophilic cytoplasm in fibrous stroma in the lamina propria and submucosa (figure 2C, D). The neuroendocrine component showed diffuse staining for synaptophysin (figure 3B) and focal staining for chromogranin A. By immunostains, both components were positive for CK7 (figure 3C), CK20 and CDx2; these findings are compatible with an adenocarcinoma of anorectal origin. Both components showed diffuse staining for p53 compatible with point gene mutation. The proliferation index by MIB1 was high (up to 70% of the tumour cells, figure 3D). The tumour cells were negative for CD55, CK5/6 and p40. The morphological appearance and immunoprofile was consistent with an MANEC of rectal origin with pagetoid spread to anal mucosa. Tp53 gene mutation is commonly found in MANECs.

Figure 1 Preoperative appearance of the ulcerated perianal rash after 7 months of topical antifungal treatment. The patient had Paget's disease of the anus with a delayed diagnosis.

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Figure 2 Microscopic examination shows two components. The adenocarcinoma component (A and B) composed of nests of cells with vacuolated amphophilic cytoplasm and moderate nuclear pleomorphism in mucin pools in the anal lamina propria or as single cells in the squamous epithelium (pagetoid spread). A few cells show signet ring cell morphology. The neuroendocrine component (C and D) shows nests, ribbons and single cells with granular cytoplasm in the fibrohyaline stroma of lamina propria and subcutaneous tissue.

Figure 3 Morphological appearance and immunostain profile confirms mixed adenoneuroendocrine carcinoma (MANEC): the adenocarcinoma component is seen on the left side and the neuroendocrine component on the right side (A). Synaptophysin is positive in the neuroendocrine component (B). CK7 stains adenocarcinoma and neuroendocrine components (C). The proliferation index by MIB1 is high focally reaching 70% of the tumour cells (D).

OUTCOME AND FOLLOW-UP

These findings represent a diagnosis of perianal Paget's disease secondary to an MANEC of the rectum. The patient was referred to an oncologist and is currently undergoing radiation therapy.

DISCUSSION

Extramammary Paget's disease (EMPD) is an uncommon lesion arising from apocrine glands of the genital and perianal regions. It is estimated to account for <1% of all anal diseases and 6.5% of all cases of Paget's disease. It is most frequently seen in

women between 50 and 70 years of age.¹ The diagnosis of this condition is often delayed because patients present with non-specific symptoms such as bleeding, pruritus, eczema or pain with defaecation. However, prompt workup and treatment is essential because such lesions may harbour an underlying malignancy, usually adenocarcinoma of the colon or rectum.²

While pure carcinoid and adenocarcinoma tumours of the colon and rectum are well characterised in the literature, less is known about MANECs. According to the WHO, such neoplasms are described as mixed when each component represents at least 30% of the lesion.^{3 4} Neuroendocrine tumours (NETs)

Learning points

- ▶ When a patient presents with itchiness, rectal bleeding and discomfort, a thorough history and physical is necessary. Diagnosis such as haemorrhoids can mislead the practitioner.
- ▶ Extramammary Paget's disease is uncommon in the anus. It is often associated with adenocarcinoma of the colon or rectum.²
- ▶ Neuroendocrine tumours (NETs) are identified as mixed when each component represents at least 30% of the tumour composition, as is the case with mixed adenoneuroendocrine carcinomas. NETs of the rectum are the second most common neuroendocrine tumours of the gastrointestinal tract. They present in the fifth decade of life, mean age of 56.⁹

of the rectum comprise ~34% of all gastrointestinal NETs and are second in incidence only to small intestinal NETs. Most patients are asymptomatic with only a minority reporting rectal bleeding, abdominal pain, weight loss or other anorectal symptoms. Most tumours are found in patients aged 50–59 with a mean age at diagnosis of 56. Among the African-American population in the USA, 27% of all NETs are diagnosed in the rectum. The incidence is two to threefold higher compared with Caucasians and is climbing among Hispanic and Asian populations as well.⁵ Although our patient is older than the mean age at diagnosis of either EMPD or MANEC of the rectum, his seemingly benign presentation was consistent with the non-specific symptoms reported in these lesions. His diagnosis and treatment were delayed by 7 months from the start of his

symptoms. This is a result of both his vague symptoms, and due to the failure of an appropriate physical examination, which includes a digital rectal examination. Clinicians may want to consider a more aggressive approach to perianal dermatitis with early biopsy to rule out a more serious underlying pathology, and all examinations should be accompanied with a digital rectal examination and/or a referral to a colorectal surgeon.

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