Signet ring cells in the gastrointestinal tract: not always what it seems

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Abstract

We describe two cases of pseudo-signet ring cells in gastric biopsies of otherwise asymptomatic adult patients. One male patient was diagnosed during follow-up of a previous intestinal type gastric adenocarcinoma and underwent surgery before recognition of this non-malignant entity. He suffered from a secondary anastomotic stenosis requiring dilatation. A second male patient was spared from surgery thanks to timely recognition by the pathologist and is still declared cancer-free until today. This extremely rare non-malignant mimicker of cancerous signet ring cells, as seen in diffuse type gastric cancer can potentially mislead the clinician. The absence of any endoscopic abnormality should prompt a revision by an experienced pathologist, digestive oncologist and surgeon to avoid unnecessary interventions and morbidity. (Acta gastroenterol. belg., **2024,** 87, **418-420**).

Keywords: adenocarcinoma, signet ring cell, upper gastrointestinal tract, surgical pathology, endoscopy.

Introduction

The pathological and clinical criteria for the diagnosis of gastric signet ring cell adenocarcinoma (SRCA) are well established. However, knowledge of a rare disease mimicker, pseudo-signet ring cells (pSRC) is not widespread among pathologists as well as gastrointestinal (GI) oncologists and surgeons. Following cases will illustrate that recognition of this entity is important to prevent a misdiagnosis of cancer which can have far-reaching consequences for the patient.

Case history

Case 1

A 59-year-old male was seen in our GI-oncology outpatient clinic four months after distal gastrectomy with perioperative fluoropyrimidine-based triplet chemo-therapy for an intestinal-type adenocarcinoma of the antrum. In the otherwise asymptomatic patient, the posterior wall of the gastric remnant showed partial thickening on follow-up CT without local tracer enhancement or metastasis on FDG-PET-CT. Endoscopically, only erythematous gastropathy was observed (Figure 1). Targeted biopsies showed the presence of signet ring cells suggestive of SRCA in the background of intestinal metaplasia. A second gastroscopy was performed. Biopsies were taken randomly from the remnant corpus and again the presence of signet ring cells was confirmed, this time in the absence of endoscopic visible mucosal lesions including magnification endoscopy (ME) or narrow band imaging (NBI). These signet

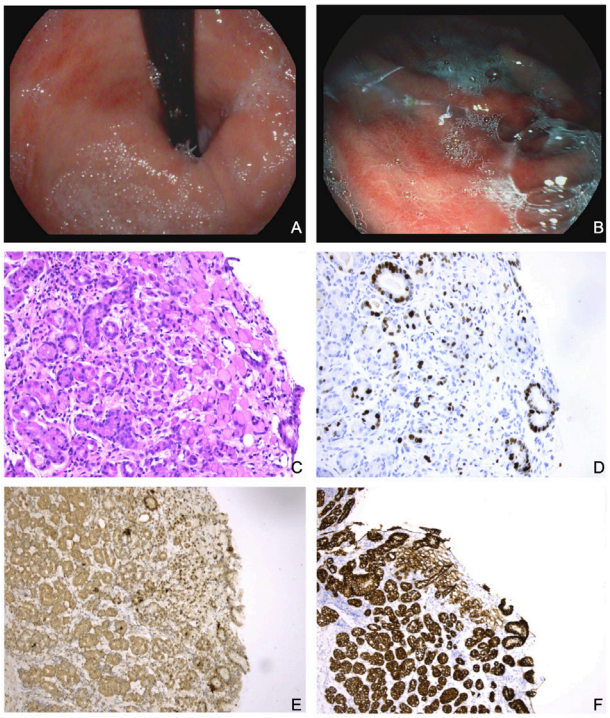

Figure 1. — Illustrations of case 1. A-B: Endoscopic image of pSRC zone. Note the isolated mucosal erythema without signs of ulceration or irregularity; C: hematoxyline-eosine stain with 200 times magnification. On the right sided surface small cluster of pSRC characterized by abundant glassy cytoplasm with crescent-shaped nuclei compressed to the periphery of the cells. They are not invading beyond the lamina propria and are not accompanied by a desmoplastic reaction; D: Ki67 staining with 200 times magnification. pSRC have a low proliferation rate; E: p53 staining with 100 times magnification. No loss of p53 in pSRC; F: E-cadherine with 100 times magnification. No loss of E-cadherine in pSRC. Abbreviations: pSRC: pseudo-signet ring cells.

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Submission date: 24/02/2024
Acceptance date: 15/07/2024

ring cells were loosely clustered, without tendency to invade the surrounding lamina propria. An epithelial origin was confirmed by *prekeratin* staining. Strikingly, the *Ki67* proliferation index was low, there was no aberrant expression of *p53* and there was no loss of *E-cadherin* expression (Figure 1). Pathologic revision of the diagnostic biopsies as well as the resection specimen of prior gastrectomy showed no presence of signet ring cells. In fact, there was no residual disease in the resection piece following neoadjuvant chemotherapy (ypT0N0). Despite the reassuring clinical findings, presence of worrying signet ring cells in a patient with a history of malignancy drove the decision to proceed to completion total gastrectomy. Pathology of the gastric remnant was negative for SRCA and pSRC. After one-year follow-up, the patient remains in remission. Surgery was however complicated with secondary stenosis of the oesophagojejunal anastomosis leading to weight loss and dysphagia, requiring a pneumatic dilation 8 months post-surgery.

Case 2

Random gastric biopsies of a 61-year-old male patient taken in another hospital during a gastroscopy for routine follow-up of a Barrett's esophagus for which he took PPI (proton-pump inhibitors) daily revealed signet ring cells at the fundus. Repeated gastroscopy was negative for any visible lesion despite extensive mapping with ME and NBI. This time signet ring cells were found in random antral biopsies. Work-up by endoscopic ultrasound and FDG-PET-CT was negative. The pathological slides were sent out to the pathology lab of a tertiary care center but results weren't awaited and neoadjuvant chemotherapy was initiated. After one administration the patient was seen in our emergency department with complaints suggestive of coronary spams due to fluoropyrimidine toxicity. In meantime both the initial pathology review and pathology review at our institution, revised the diagnosis as pSRC with the same histological features as the first case. After thorough discussion with the patient, it was decided to interrupt the oncological treatment. Six weeks later a dedicated gastroscopy was performed and neither SRCA nor pSRC were found despite extensive mapping biopsies. One year later, a fourth and final meticulous gastroscopy showed again no endoscopic or pathological abnormalities.

Discussion

We present two cases of patients initially diagnosed and treated as if they were suffering from a diffuse type of gastric cancer known for its dismal prognosis. Because these pseudo-signet ring cells have the potential to mimic their malignant counterpart, cancerous signet ring cells, they were not timely recognized consequently leading to unnecessary comorbidity of respectively anastomotic stenosis and chemotherapy related toxicity.

Figure 2. — Assumptions on pathogenesis of pSRC, clockwise: geographical spread, chronic inflammation, EMR resection site, torsion of big polyps leading to ischemia, H. pylori, PPI. *Abbreviations*: pSRC: pseudo-signet ring cells, EMR: endoscopic mucosal resection, PPI: proton-pump inhibitors.

On a histological level pSRC differ from neoplastic signet ring cells in their infiltrative growth pattern (1). Typically, pSRC are grouped in well circumscribed cell clusters residing in between normal fundic glands not disturbing its configuration or architecture. There is no invasion into the lamina propria or dense surrounding desmoplastic stromal reaction. On a cellular level pSRC show bland cytologic features characterized by abundant glassy cytoplasm with crescent-shaped nuclei compressed to the periphery of the cells. On close examination the nuclei have no atypia and very rarely mitotic or apoptotic cells are seen. On immunohistochemical level, SRCA show *p53* mutation, lack *E-cadherin* expression, and exhibit increased cell proliferation, translated by a high level of *Ki67* expression. Whereas pSRC, being non-neoplastic differentiated epithelial cells without loss of epithelial *E-cadherin* staining, exhibit limited to no cell proliferation, and no *p53* tumor suppressor gene mutation as illustrated by our two cases (2). Distinct histological hallmarks helpful for the differential diagnosis are listed in table 1.

The presence of pSRC observed in the first case could be a result of residual inflammation secondary to prior surgery since pSRC are described in chronic inflammatory states such as H. pylori associated gastritis, peptic ulcer disease and ischemic states (Figure 2) (3-7). Alternatively, neuroendocrine cell hyperplasia in the background of intestinal metaplasia could have histologically been mistaken for signet ring cells since neuroendocrine cells can share signet ring cell features (8). Notably, it's the presence of intestinal metaplasia that should have raised suspicion on correct diagnosis of concomitant SRCA since intestinal metaplasia is a

Table 1. — **Histological features of pseudo-signet ring cells compared to signet ring cell adenocarcinoma**

	pSRC	SRCA
Size of the mucus vacuole	Variable size, usually large	Small
Border of the mucus vacuole	Well defined	Ill defined
Nuclear size	Small	Enlarged
Nuclear shape	Curved	One side is usually flat
Growth pattern	Well circumscribed clusters	Individually infiltrative
Abbreviation: pSRC: pseudo-signet ring cell, SRCA: signet ring cell adenocarcinoma		

malignant precursor of the molecularly distinct intestinal type of gastric cancer (9,10). Why these pSRC weren't present in the totalization gastrectomy specimen isn't clear but it seems that the presence of pSRC waxes and wanes over time, as is also illustrated in the second case in which subsequent gastroscopies didn't reveal any residual pSRC. A plausible hypothesis for pSRC presence in this second case could be the chronic use of PPI in the context of Barrett esophagitis. Signet ring cell changes, associated to chronic PPI use are attributed to irreversible binding of PPI causing dilated secretory canaliculi within the parietal cells giving them their typical signet ring cell appearance (11).

Scientific literature on pSRC mainly consists of scarce case reports, some of them similarly describing unnecessary interventions when not timely recognized as being non-malignant (1,12,13).

These and our case series highlight the further need of awareness of this diagnostic pitfall amongst clinicians diagnosing and treating patients with gastric cancer. For correct histological diagnosis immunohistochemical studies are useful. However, in adjunction to pathology it is important to incorporate the bigger clinical picture, especially the absence of any endoscopic red flags (for example ulcers, masses) using advanced techniques such as ME and NBI should raise suspicion of its presence. Pathology revision and eventual new biopsies at a relative distance in time (6-8 weeks as in our 2 cases) can be advised in case of doubt.

Conflict of interest

All authors declare that they have no conflicts of interest.

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