

Histopathology and Immunohistochemical Examinations in Adenosquamous Carcinoma, Cancer of the Stomach - Case Study

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1. Abstract

The authors present a case of gastric adenosquamous carcinoma in a 62-year-old female patient. A month earlier, an adenocarcinoma infiltration was diagnosed during gastroscopy in the histopathological examination of specimens from the pyloric ulcer.

Intraoperatively, a large tumor of the pylorus was found with a perforation hole on the posterior wall of the stomach. Subtotal gastrectomy was performed with D2 lymphadenectomy, Billroth II colonic anastomosis, and Braun's enzyme anastomosis.

The material from the lymph nodes, the stomach and the omentum was sent for histopathological examination. An ulcerated tumor was found in the pyloric area of the mucosa with raised edges corresponding to type 2 of advanced gastric cancer.

In the surgical material from gastric resection, we found a structure of adenosquamous carcinoma, and according to Lauren's classification, it was type I of limited gastric cancer. Metastatic cancer was found in 17 out of 30 lymph nodes encountered. In lymph node metastases, all forms of primary tumor tissue have been encountered. According to the TNM classification of 2019, the cancer advancement stage is: pT3 pN3b.

In the immunohistochemical examination of the material taken from the primary tumor and tumor metastases, the expression of CK7+ was found in the glandular and mucous components.

Nuclear expression of p63+ and p40+ was only present in the squamous component. No CD56, synaptophysin or chromogranin expression was found in the neoplastic cells tested. The determination of the HER-2 protein in the cells of the neoplastic infiltration of the stomach wall was negative (score = 0).

2. Introduction

Gastric cancer is still a major diagnostic and therapeutic problem. In 2020, 768,793 deaths were reported worldwide due to this cancer, which is the fourth most frequent cause of death due to neoplastic disease [1]. In Poland, this neoplasm is the fifth cause of death due to neoplastic diseases in men and eighth in women [2].

A definitive diagnosis of gastric tumours requires microscopic confirmation. The vast majority of gastric cancers are adenocarcinomas, other types of this cancer occur sporadically. For example, adenosquamous carcinoma of the stomach accounts for 0.2-0.25% of all cancers of this organ [3, 4]. Only a few case reports of this disease [5-7] and comprehensive studies using large case series [8-12] were found in the analyzed literature. It is also rare to find publications on the usefulness of immunohistochemical tests for the diagnosis of adenosquamous carcinoma [7, 13, 14]. The authors decided to submit for publication a case of gastric adenosquamous carcinoma, diagnosed on the basis of a histopathological examination using a panel of immunohistochemical tests.

3. Case Presentation

A 62-year-old female patient was urgently admitted to the hospital due to sudden, severe abdominal pain, mainly in the epigastric region. On admission, the laboratory parameters are normal, and the abdominal X-ray is without signs of obstruction or perforation.

Among the earlier, she underwent an endoscopy of the upper gastrointestinal tract. An ulcer was found within the pylorus and an adenocarcinoma infiltration was diagnosed in the histopathological examination of the specimen collected from this ulcer. Due to the features of peritonitis, a computer tomography of the abdominal cavity was performed, in which a perforated tumor of the pylorus was diagnosed and the patient qualified for urgent surgery.

A large tumor of the pylorus was confirmed intraoperatively with a perforation hole on the posterior stomach wall. Subtotal gastric resection was performed with D2 lymphadenectomy, Bilroth II colonic anastomosis, and Braun's jejunum anastomosis. Postoperatively, good convalescence, decreasing inflammation indicators and no signs of anastomotic leak were observed. The patient was discharged home in good psychophysical and local condition.

For histopathological examination (No. 1431/19 Department of Pathomorphology, MEDICAM Specialist Hospital in Gryfice), the material was obtained in three vessels. The first material was collected from lymph nodes in the area of the celiac trunk and the second material from the lymph nodes in the area of the hepatic ligament. The third material is a sewn-up fragment of the stomach, which, after being cut along the greater curvature, had dimensions of 18 x 10 cm, with an adjoining omentum of 26 x 24 cm. In the mucosa in the pyloric area, an ulcerated tumor with perforation and 4 x 4.5 cm rolled rims was found, infiltrating the entire thickness of the stomach wall. The above macroscopic picture corresponds to type 2 of advanced gastric cancer (ulcerated tumor with clearly delimited, raised margins undermining the mucosa) according to the Japanese Research Association for Gastric Cancer classification [15, 16]. The tumor was located macroscopically 1.8 cm from the distal line of the surgical incision.

The material for histopathological examination was collected according to the recommendations of the Polish Society of Pathologists [16], taking into account in the third material: the boundaries of the surgical incision from the cardia and duodenum, the stomach wall with the tumor, the surrounding lymph nodes, the gastric omentum and the wall of the stomach outside the tumor.

Routine histological examination of H&E stained specimens and immunohistochemistry with the use of the following markers: CK7, p63, p40, CK20, CD56, synaptophysin, chromogranin A, and Ki-67 were performed on the material under review, fixed in 4% buffered formalin and embedded in paraffin. Histopathological diagnosis was made on the basis of the 2019 WHO classification and the recommendations of the Polish Society of Pathologists [3, 16].

The paraffin-embedded immunohistochemical materials were cut into 4 micrometer sections and mounted on glass slides with an adhesive coating - SuperFrost® Plus (Menzel Gläser®). Subsequently, these sections were machine stained (BenchMark ULTRA IHC/ ISH System - Roche Diagnostics instrument) based on validated diagnostic protocols and reagent kits prepared by Roche.

HER-2 protein was also determined in the neoplastic infiltration using the rabbit antibody Ventana PATHWAY HER-2/neu (4B5), sections for this study were also machine stained based on the diagnostic protocol and reagent kit prepared by Roche.

In the histopathological examination of the material collected from the lymph nodes in the area of the visceral trunk, metastasis of tubular adenocarcinoma was present in one of the 4 lymph nodes with infiltration of the capsule and surrounding adipose tissue. Reactive changes were found in the remaining 3 lymph nodes, free from tumor metastases.

In the histopathological examination of the material collected from 3 lymph nodes in the area of the hepatic ligament, no tumor metastases were found, only reactive changes were present.

In the surgical material from subtotal gastrectomy, adenocarcinoma (WHO) was found within the pyloric tumor (Figure 1). The squamous cell component constituted 30% of the neoplastic structure and the adenocarcinoma component 70% of its fabric, including 60% of the infiltration of tubular adenocarcinoma and 10% of mucinous adenocarcinoma. According to Lauren's classification, it was type II limited stomach cancer. The neoplastic infiltration covered the entire thickness of the stomach wall and spread to the surrounding adipose tissue without engaging the visceral surface of the serosa. Angioinvasion was present. Infiltration along the nerves was not encountered.

Neoplastic metastases with infiltration of the capsule and the surrounding fatty tissue were found in 16 out of 23 lymph nodes encountered. However, in 7 out of 23 lymph nodes only reactive inflammatory changes were found. In lymph node metastases, all three primary tumor forms were found: tubular adenocarcinoma in 7 nodes, mucinous adenocarcinoma in 3 nodes, adenocarcinoma in 4 nodes (Figure 2) and squamous cell carcinoma in 2 nodes. No neoplastic infiltration (R0) was encountered in the proximal, distal and radial cutting lines. Apart from the tumor, no neoplastic infiltration was found in these sections taken from the gastric omentum and the wall of the stomach. According to the TNM classification of 2019 (3), the cancer advancement is: pT3 pN3b.

An immunohistochemical examination was performed on the material collected from the primary tumor and neoplastic metastases. Cytoplasmic expression of CK7+ was found in the glandular and mucous component carcinoma of the stomach (Figure 3). Nuclear expression of p63+ was found in the squamous cell component of gastric carcinoma (Figure 4), and p40+ was also found in the nuclei of neoplastic cells in the squamous cell component carcinoma of

the stomach (Figure 5). On the other hand, cytoplasmic expression of CK20+ was focal in mucinous component of gastric carcinoma. No CD56, synaptophysin or chromogranin expression was found in the neoplastic cells tested. The Ki-67+ proliferation index was 60% of the nuclei in the weaving of adenocarcinoma, about 50% of the nuclei in the weaving of mucinous adenocarcinoma, and 40% of the nuclei in the weaving of the squamous cell carcinoma. It should be noted that the results of immunohistochemical tests were identical in the material collected from the primary tumor and in the material collected from the lymph node metastases. The determination of the HER-2 protein in the cells of the neoplastic infiltration of the stomach wall was negative (score = 0).

No significant microscopic changes or colonization of *Helicobacter pylori* were found in the gastric mucosa in the vicinity of the tumor (the slides were stained by histochemistry according to Giemsa and immunohistochemistry).

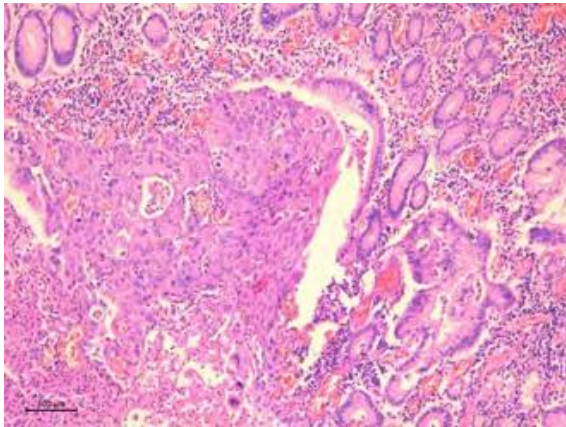


Figure 1: Infiltration of adenosquamous carcinoma in the gastric submucosa. H&E. 100x magnification.

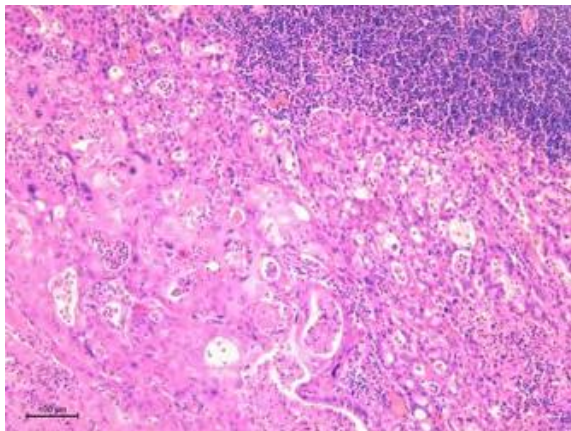


Figure 2: Metastasis of adenosquamous carcinoma to the lymph node. H&E. 100x magnification.

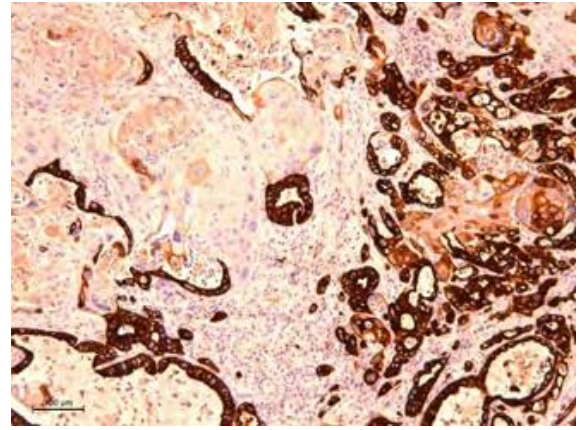


Figure 3: Metastasis of adenosquamous carcinoma to the lymph node. Immunohistochemical cytoplasmic expression of CK7 in the glandular component of the tumor. CK7. 100x magnification.

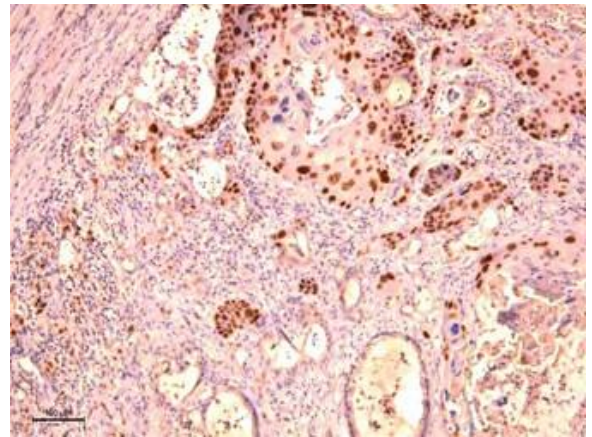


Figure 4: Metastasis of adenosquamous carcinoma to the lymph node. Nuclear immunohistochemical expression of p63 in the squamous component of cancer. p63. 100x magnification.

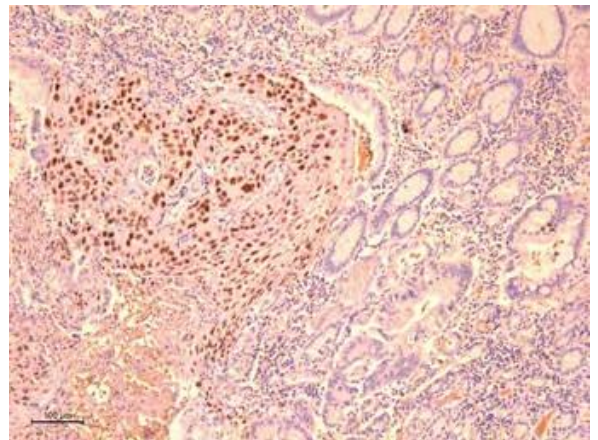


Figure 5: Infiltration of adenosquamous carcinoma in the gastric submucosa. Nuclear immunohistochemical expression of p40 in the squamous component of cancer. p40. 100x magnification.

4. Discussion

The neoplastic infiltration of the pyloric tumour, in our case, consisted of a mixture of adenocarcinoma and squamous cell carcinoma with a gradual transition between them. According to WHO 2019, adenosquamous carcinoma of the stomach is a primary cancer of the stomach, consisting of both glandular and squamous elements, with the squamous element accounting for $\geq 25\%$ of the tumour [3]. In our case, the squamous component accounted for 30%, and therefore the neoplasm met the criteria for the histopathological diagnosis of adenosquamous carcinoma.

In an endoscopic examination of the upper gastrointestinal tract performed before the surgery, adenocarcinoma was diagnosed in sections taken from the ulcer. This is because in our case, adenocarcinoma (70% of weaving) dominated in the neoplastic infiltrate over squamous cell carcinoma (30% of weaving). Thus, biopsy diagnosis of adenocarcinoma or squamous cell carcinoma of the stomach does not exclude adenosquamous carcinoma [6, 9, 11].

The most common site of gastric adenosquamous carcinoma is the lower third (45% of cases), followed by the upper and middle parts [3, 12]. In our case, the tumor infiltration was located in the pylorus, i.e. in the lower third of the stomach.

Adenosquamous carcinoma of the stomach is usually associated with poor postoperative prognosis (8,9,10). This neoplasm is usually first diagnosed at a high stage. The diameter of the neoplastic infiltration is in most cases about 5 to 6 cm, and in 53% of cases, the neoplasm is first diagnosed at the pT4 stage according to the pTNM system. At the time of detection, as many as 86% of cases are metastatic to the lymph nodes. Lymph node metastases mainly originate from the adenocarcinoma component, but the squamous component or both may be evident in metastasis [3, 12].

In the case described by us, all the above-mentioned features indicate a bad prognosis. In the pyloric region of the stomach, an ulcerated tumor with perforation and 4 x 4.5 cm rolled edges was encountered. Neoplastic metastases were found in 17 of 30 lymph nodes encountered. In 11 lymph nodes the metastases were adenocarcinoma, in 4 adenosquamous carcinoma and in 2 squamous cell carcinoma. According to the 2019 WHO classification, the cancer stage was defined as: pT3 pN3b (3).

The aggressiveness of this neoplasm is also evidenced by a case report of an early adenosquamous carcinoma with numerous metastases to the lymph nodes and rapid generalization of the neoplastic disease following surgery [7].

In the differential diagnosis of gastric tumours, an antibody panel is used to determine the histological type of cancer or gastric sarcoma [17]. An essential criterion for the diagnosis of adenosquamous carcinoma is confirmation of true differentiation of glandular or mucous cells by immunohistochemistry, and the squamous component should show all cytological and architectural features of squamous cell carcinoma [7, 13, 14]. The presence of adenoma-

tous or microcystic lesions in pure squamous cell carcinoma is not sufficient for such a diagnosis (3).

In the presented case, the immunohistochemical test confirmed the diagnosis of adenosquamous carcinoma. Cytoplasmic expression of CK7+ was found in the glandular and mucous components of carcinoma of the stomach. Nuclear expression of p63+ and p40+ was found only in the squamous cell component of gastric carcinoma. On the other hand, cytoplasmic expression of CK20+ was focal in gastric mucinous adenocarcinoma component. No CD56, synaptophysin or chromogranin A expression was found in the neoplastic cells tested.

In recent years, the Trastuzumab therapy has been introduced into the treatment methods of patients with gastric cancer. This therapy may be effective in patients with HER2 gene amplification associated with HER2 protein overexpression through immunohistochemistry. Unfortunately, in the available literature, and in our case, no immunohistochemical expression of HER2 in adenosquamous carcinoma cells was found, which limits the use of effective adjuvant chemotherapy in these patients [13, 16].

5. Conclusion

For the correct histopathological diagnosis of gastric adenosquamous carcinoma, it is necessary to perform, in addition to the routine histological examination, immunohistochemical tests for the components of this tumor.

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