

Adenosquamous Cell Carcinoma of the Stomach ¹⁸F-FDG PET/CT Diagnosis and Review of Literature

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Abstract

Adenosquamous carcinoma of the stomach (ASCS) is extremely rare with less than one hundred cases published in the world literature. It is defined by combined adenocarcinoma and squamous cells carcinoma of the stomach. ASCS is clinically aggressive and has a poor prognosis, even when discovered at an early stage. This intriguing entity is characterized by non specific symptoms or radiological signs. Integrate ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography ¹⁸F FDG.PET/CT is useful morphologic and functional modalities for evaluating primary tumor, local extend and invasion beyond gastric wall or distant metastatic and eventually for management. Diagnosis of ASCS requires immunohistochemical confirmation. We report a 77-year-old man who was admitted to hospital because of epigastric pain, vomiting and melena since more than a month. Gastroscopy with biopsies had initially suggested gastric squamous cell carcinoma .Thoracic and abdominal computed tomography scan (CT) showed a huge mass in the gastric body, largely necrotic, infiltrating the adjacent structures without metastases. Partial gastrectomy with resection of the proximal 2/3 of the stomach, the spleen, the body and tail of pancreas and the left transverse colon was performed. Immunohistochemical analysis demonstrated ASCS with mixed adenocarcinomatous and squamous cells carcinoma with invasion of gastric lymph nodes. Unfortunately, two months after surgery, a CT of the abdomen revealed diffuse metastasis and the patient died three months later. In light of this case, we discuss the pathogenesis, staging and monitoring of this rare entity by combined (18)F-FDG PET/CT with review of the literature.

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Key words: adenocarcinoma, squamous cell carcinoma, Stomach, pathogenesis, (18)F-FDG.PET/CT, immunohistochemical.

Received : September 29 , 2016; **Accepted :** October 18 , 2016; **Published :** November 01 , 2016;

Introduction

Adenosquamous carcinoma (ASCS) is an exceedingly rare neoplasm of the stomach. This tumor consists in varying proportions of adenocarcinoma and squamous cell carcinomas. The incidence of this entity varies between 0, 04 and 0, 07% of gastric cancer and less one hundred cases are described in the literature. We present one case of ASCS in a 77 year-old man. In light of this observation we discuss than several hypothesis of pathogenesis and the fundamental role of combined fluorine-18 fluorodeoxyglucose imaging PET and computed tomography (18F-FDG.PET/CT) in staging and monitoring this unusual tumor.

Case report

A 77-year-old man was admitted to hospital because of epigastric pain, vomiting and melena since more than a month. The patient's past medical history included hypertension, biological aortic valve replacement, right parotidectomy for cystadenolymphoma, pulmonary embolism and surgery for inguinal hernia. Physical examination demonstrated abdominal distension, painless on palpation but no mass palpable and nor organomegaly. Routine laboratory tests revealed a normocytic, normochromic anemia (hemoglobin 107 g/l) and mild thrombocytopenia as well (platelets 141 G/l). All other laboratory exams were normal.

Abdominal CT scan with intravenous contrast material enhancement showed a huge mass of the gastric body, largely necrotic, infiltrating the pancreatic tail, the spleen and the left transverse colon. CT scan did not reveal any other lesion than the except gastric tumor (figure 1: A, B).

Gastroscopy revealed a large (7x 8 cm) gastric tumor, starting from the cardia to less than 1 cm above the hiatus, located along the lesser curvature of the stomach, with ulceration and easily bleeding. Biopsies

were performed and the histological findings concluded a moderately differentiated squamous cell carcinoma, keratinizing of undetermined origin.

18F-FDG PET-CT with injection of intravenous iodinated contrast demonstrated an intense and diffuse hyper metabolism at the primary tumor of the stomach. No morphological or metabolic argument features of secondary manifestation of this tumor were observed in the whole-body (Fig 2). Partial gastrectomy with resection of the proximal 2/3 of the stomach, the spleen, the body and tail of pancreas and the left transverse colon was performed.

A macroscopic exam revealed a large (12 cm) gastric ulcerated tumor, infiltrating the entire gastric wall, the pancreas, the lesser omenta, the spleen parenchyma and the colonic wall (Fig 3: A,B).

Microscopically, the tumor proliferation consisted mainly of islands and nests with a squamous differentiation, composed of large cells with slightly abundant eosinophilic cytoplasm and enlarged pleomorphic nuclei, with irregular contours, coarse chromatin and prominent nucleolus. There was presence of some mitotic figures, dyskeratotic cells and foci of keratinization. Focally, there was formation of small glandular structures with some isolated cells with vacuolated cytoplasm and showing mucus secretion. Immunohistochemical analysis showed a weak nuclear positivity for P63 in the squamous portion of the lesion with obvious negativity of adenocarcinomatous cells. Cytokeratin 5/6 also showed a clear membrane and cytoplasm positivity in the squamous component, the adenocarcinoma component remaining negative. Cytokeratin 7 was positive in both components and cytokeratin 20 showed few positive cells (fig 4: A, B, C, D). Among 32 regional lymph nodes examined, there were four lymph nodes with metastasis. The TNM classification (according to the seventh edition UICC 2009) was therefore pT4b pN2 (4/32) V1 L1 Pn1.



Figure 1: A and B, Abdominal CT scan with intravenous contrast enhancement showed a huge mass of the gastric body, largely necrotic, infiltrating the pancreatic tail, the spleen and the left transverse colon. CT scan did not reveal any other lesion except the gastric tumor. C: Multiples liver metastases two months after surgical operation.

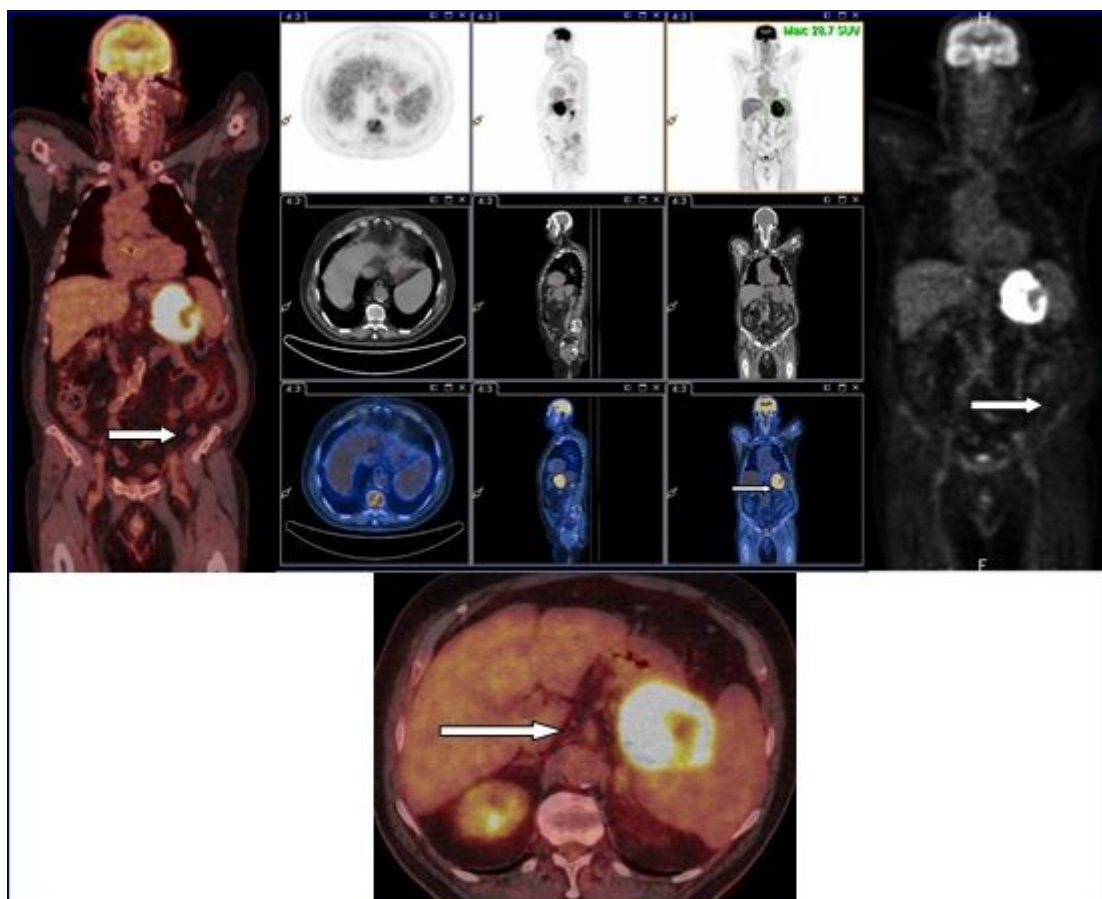


Figure 2: 18F-FDG PET-CT with injection of intravenous iodinated contrast demonstrated an intense and diffuse hyper metabolism at the primary tumor of the stomach. No morphological or metabolic argument features of secondary manifestation of this tumor were observed in the whole-body.



Figure 3: A-Macroscopic aspect: "En bloc" resection of stomach, spleen and omentum, with a part of pancreas and colon (not shown on this photograph). The stomach has been opened to show the tumor. B-Macroscopic aspect: Large tumor with macroscopic infiltration of stomach wall, omentum, pancreas and spleen.

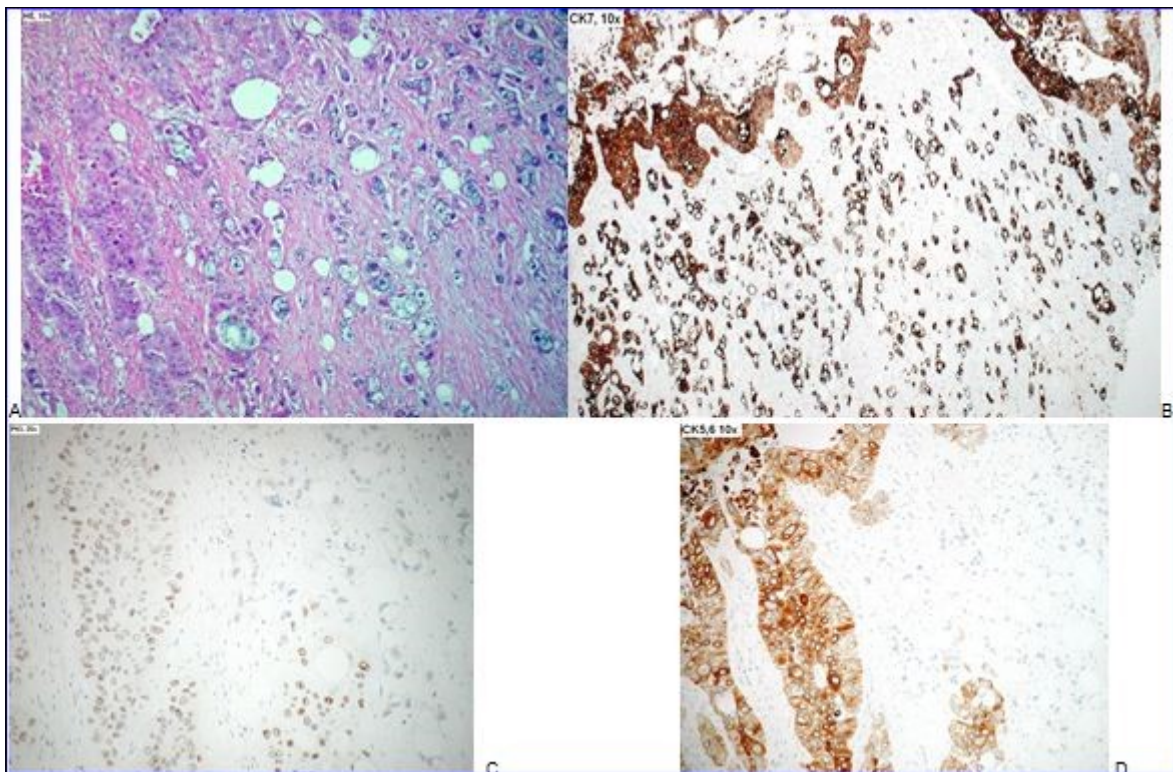


Figure 4: A-95% of tumor is a poorly differentiated squamous carcinoma with rare foci of keratinisation, and <5% of tumor is a poorly differentiated adenocarcinoma, with some isolated cells. B-Both components, squamous carcinoma and adenocarcinoma, are Cytokeratine 7 positive. C- Squamous component shows a nuclear positivity for P63, with negativity of the adenocarcinoma. D-Cytokeratine 5, 6 is positive in the squamous component, but not in the adenocarcinomatous component.

Follow-up thoracic-abdominal CT scan obtained two months after surgical operation showed liver and lung metastasis and multiple retroperitoneal lymph nodes (Fig 1, C). Palliative chemotherapy was then indicated. Unfortunately, the patient's condition deteriorated rapidly and he expired three months later.

Discussion

Among carcinomas of the stomach, adenocarcinomas are the most prevalent type, and adenosquamous carcinoma (ADSC) or squamous cells carcinoma are exceedingly rare representing respectively 0.07 and 0.04 % of all gastric carcinomas, according to the WHO criteria of histological classification of stomach tumors (1). These aggressive tumors occur in patients with an average age between 50 and 70 years and with a male-female ratio 4:1 (2).

ASCS consists a mix of varying proportion of adenocarcinoma cells and squamous cells carcinoma, but the later component by definition should exceed 25% of tumor gastric mass (3). This entity is most commonly developed at the sites where adenocarcinoma typically arise such as stomach, intestine (4) and uterus (5) but it's reported in the esophagus (6), anus and vagina where squamous cells carcinoma are more frequently encountered.

Many authors now believe that this kind of carcinoma results from two theories, either transforming or collision (7). In the first one, the adenocarcinoma is transforming into squamous cells carcinoma. The collision theory proposes that adenocarcinoma and squamous cell carcinoma arise independently from different sites and ultimately coalesce (8).

Furthermore, Boswell and Helwig (9) considered these following criteria to allow the diagnosis of SSC: 1. Keratinizing cells with typical pearl formation, 2. Mosaic pattern of cells arrangement in which cell borders are sharp, 3. Intercellular bridges and 4. High concentration

of sulfhydryl indicates the presence of keratin or prekeratin.

In spite of that, the exact histogenesis of the ASCS is not yet clear; however, multiple hypotheses are postulated (10): 1. Squamous metaplasia of an adenocarcinoma; 2. Cancerization of metaplastic non neoplastic squamous cells; 3. Cancerization of ectopic squamous epithelium; 4. Differentiation of multipotential undifferentiated cancer cells toward both squamous and glandular cells and 5. Collision of concurrent adenocarcinoma and squamous cell carcinoma.

Our present case seems to support these hypotheses theories for 4 reasons: the tumor showed keratinizing cell masses, mosaic patterns, intercellular bridges and adenocarcinoma components.

Preoperative diagnosis of ASCS of the stomach is difficult and is challenging. There are no specific clinical symptoms or defining radiological imaging that would differentiate this neoplasm from the more common gastric tumors.

The symptoms are nonspecific including vague abdominal pain, melena, diarrhea and weight loss (11) and ASCS is usually found at an advanced stage with invasion of the neighboring structures with local lymph nodal and other organs metastasis.

The American Joint Committee on Cancer (AJCC), staging system is widely used for the characterization of disease, burden and prognosis in gastric cancer (12). Thereby, the combined 18F-FDG PET/CT may be useful in the preoperative assessment and therapeutic monitoring of patients with gastric cancers (13). It helps in detection of primary tumor; extension of disease in stomach and surrounding structures, local and distant lymph node and solid organ metastasis and peritoneal dissemination (14).

Over the last two decades, thin section with multiplanar reconstruction CT scan combined to 18F-FDG PET have dramatically increased the impact of management of gastric tumors at different stages. Correlating anatomic information and functional modalities help for diagnosis, pre operative staging of the ASCS and for monitoring treatment effect.

CT scan is an accurate anatomical imaging for determination of preoperative T stage. In spite, 18F-FDG PET cannot be helpful in determined the exact T stage because prominent uptake averaged across several millimeters, a distance too great to give confidence when assessing barrier invasion on the surface of organs such as present case (15).

Moreover, CT Scan identify positive lymph nodes metastasis based on size, shape, central necrosis and heterogeneity confirms metastatic involvement in stage I and II but cannot distinguish between reactive hyperplasia or metastatic enhancement (15). Whereas, 18F-FDG PET detects lymph node metastases in stage III and IV beyond compartment I and II and also small lymph nodes (less than 1 cm) which are metabolically active of metastatic disease (16).

For metastases, 18F FDG PET may be more accurate than the anatomical imaging modalities in the detection of metabolic distant metastases, and liver metastases smaller than 1 cm missed during the portal venous or arterial phase on CT scan (17). The limitations of 18F FDG PET are not tumor-specific as it is also positive by inflammatory cells or peritoneal metastases (18) and small lung metastases (less than one cm) (18). In a recent study (19), the sensitivity of CT and 18F-FDG PET in the evaluation of pulmonary nodules was 93% and 57%, respectively.

Despite technical advances in gastroenterology and imaging in the early detection of ASCS, the diagnosis is often made after the tumor has already metastasized to the regional and distant lymph nodes,

liver or lung, such as in our patient. Accurate preoperative diagnosis of ASCS is made with great difficulties since there are no imaging studies that would differentiate it from squamous cell carcinoma, adenocarcinoma, lymphoma, gastrointestinal stromal tumor (GIST) or more benign stomach neoplasm (20). In any case the diagnosis of ASCS is mainly based on the histological exams and requires immunohistochemical assessment of tumor tissue.

Complete resection of the gastric tumor and adjacent lymph nodes represents the only effective curative treatment (21). The role of radiotherapy and chemotherapy after surgery is controversial but suggested by some authors to reduce the risk of recurrence (22).

Despite the recent advances in diagnosis and therapy, the mortality with ASCS remains substantial. Patient's outcome after resection of ASCS is generally poor. The typically advanced stages at the time of initial diagnosis explain this outcome. ADSC of the stomach is more aggressive than other histological types of gastric carcinomas (23). The median survival from the time of diagnosis is shorter than for adenocarcinoma and squamous cell carcinoma (24). Moreover, ASCS has a high rate of early metastases despite good differentiation (25).

It is not surprising that survival was not prolonged in our patient who had an ASCS and a rapid systemic metastasis less than three months after.

Conclusion

The ASCS is a rare malignancy, characterized by a particularly aggressive potential and poor prognosis. It is often found at the stage of digestive complications with extensive visceral invasion and metastasis. Early diagnosis of ASCS has important implications for surgical management at presentation and afterward. The combined use of CT and 18F-FDG PET may be useful in

the preoperative staging and helpful in the follow up of patients undergoing chemotherapy but the diagnosis remains based on immunohistochemical exams.

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