

Two cases of sudden death due to pulmonary tumor thrombotic microangiopathy caused by occult gastric carcinoma

M. BEN KHELIL^{1,3}, Y. CHKIRBENE^{1,3}, H. AZZOUZ², S. HAOUET^{2,3}, M. HAMDOUN^{1,3}

¹ Department of Forensic Medicine, Charles Nicolle Hospital, Tunis, Tunisia; ² Department of Pathology, La Rabta Hospital, Tunis, Tunisia; ³ Faculty of Medicine, University Tunis-Elmanar, Tunis, Tunisia

Key words

Forensic Pathology • Sudden death • Pulmonary tumor thrombotic microangiopathy • Gastric cancer • Autopsy

Summary

We present two cases of occult gastric carcinoma associated to a large pulmonary tumors thrombosis microangiopathy (PTTM). The first case is a 28 years-old man. He was dead due to a respiratory failure. Autopsy showed a whitish indurated mass invading the stomach wall. Histological findings showed a primary “signet ring” gastric adenocarcinoma with pulmonary carcinomatosis and multiple PTTM and a heart metastasis.

The second case is a 24 years-old pregnant woman. The main symptoms were nausea and stomach discomfort and they were seen as pregnancy signs. She was dead because of respiratory failure, 10 hours after a vaginal delivery. Autopsy showed the absence of any cause of death related to the delivery and the presence of a whitish indurated mass in the stomach. Histological findings showed a primary “signet ring” gastric adenocarcinoma, with pulmonary carcinomatosis and multiple PTTM.

Introduction

Gastric cancer is known to be a silent neoplasia, discovered in most of the cases at advanced stages. Forty percent of the patients never report dyspeptic symptom¹. About two third of patients are diagnosed with advanced cancers at initial presentation^{2,3}. In spite of the advances made in the radiological and endoscopic fields that induced the improvement in treatment modalities, gastric cancer remains one of the leading cancer-related death illnesses with approximately 700,000 deaths per year³⁻⁵. Many authors reported cases of gastric cancer revealed by a sudden unexpected death⁶⁻⁹. In fact, Chinen and coworkers⁶, reported 28 cases of sudden death among 2308 autopsies of patients with malignancies. Five cases occurred in patients with gastric carcinoma. In such cases, death was supposed to be caused by cardio vascular complication rather than ischemic heart disease⁶. Cardiovascular complications included pulmonary hypertension and cor pulmonale that are related to pulmonary tumor thrombotic angiopathy (PTTM)⁷⁻⁹. PTTM, first described by Von Herbay¹⁰, is characterized by tumor micro emboli associated with fibro cellular and fibro

muscular intimal proliferation in small arteries and arterioles of the lung⁷. It is a rare complication with 48 reported cases in a literature review published in 2010⁷. A study conducted in Japan over a 28 years period identified 18 cases of PTTM complicating a gastric cancer over 2,215 autopsy cases of patients having a malignant cancer¹¹. PTTM is known to be caused in most of the cases by gastric carcinoma which is mainly a poorly differentiated adenocarcinoma or a signet ring cell type. Its incidence varies between 17 and 26,5%⁶⁻¹².

We report two cases of sudden death caused by pulmonary hypertension related to a PTTM and organic metastasis due to an occult gastric carcinoma.

Cases reports

CASE 1

A 28-years-old Tunisian man without particular past medical history who complained dysphagia to both solids and liquids, asthenia, anorexia and emaciation in two months. He was admitted for exploration. Physical examination did not show any specific sign except cachex-

Acknowledgements

The authors wish to thank Mr Slim Guizani for his valuable help in the English editing of the manuscript.

Correspondence

Mehdi Ben Khelil, 20 Rue Ahmed Khairedine, Le Bardo, 2000 Tunis - Tel. (00216) 97.40.29.19 - Fax (00216) 71.56.13.65 - E-mail: benkhelilmehdi@yahoo.fr

ia (body mass index: 18). Laboratory tests revealed mild anemia (hemoglobin, 10.8 g/dL; hematocrit, 31.2%) and an elevated serum level of C-reactive protein (22.4 mg/dL). The other values were within normal levels (serum albumin level was not measured because he died quickly after being hospitalized). Radiological (Abdominal computed tomography) and esophageal-gastric endoscopy were planned. The patient had sudden dyspnea 20 hours after being hospitalized (Respiratory frequency: 44 cycle. min⁻¹) with a rapid respiratory failure and then died of heart attack.

Autopsy showed no specific signs at the external examination of the body. Dissection showed:

- nonspecific signs of asphyxia;
- multiple peri-pulmonary and aortic nodes;
- multiple whitish masses in both lungs giving the aspect of a military localizations;
- a 2.5 cm² whitish masses on the posterior wall of the left ventricle at 3.5 cm above the tip of the heart;
- two indurated nodes (1 and 2 cm) on the splenic hilum;
- a whitish indurated mass of 15 cm, invading the whole stomach wall starting from the cardia and going along the greater curvature;
- right ventricular dilatation.

Microscopic examination showed a primary gastric carcinoma with only signet-ring cells with no adenocarcinomatous component (Fig. 1 a,b). The tumor infiltrated the aortic wall, the lung, the heart, the spleen and the mediastinal lymph nodes. Lung localization was characterized by multiple nodules. Moreover we found multiple localizations of pulmonary tumor thrombotic micro and

macro angiopathy (PTTM) (Fig. 2 a, b) which caused a neoplastic obstruction of about 80% of pulmonary small arteries and arterioles. The latter were often associated with fibrocellular and fibromuscular intimal proliferation in the lung arteries (Fig. 2 c, d). Immunohistochemistry was not applied.

Post mortem toxicological investigations were negative. Death was considered to be the consequence of an acute heart failure due to metastatic gastric carcinoma with multiple pulmonary tumor thrombotic microangiopathy (PTTM) and metastasis in the left ventricle.

CASE 2

A 24 -year-old woman with no previous history of malignancies or other chronic diseases was pregnant when she presented with nausea and stomach discomfort. Her pregnancy was well monitored by a gynecologist. She had a normal vaginal delivery (gave birth to a boy, Apgar score 1min: 8/ 5min: 9, weight at birth 3100g). Ten hours after the delivery she presented sudden dyspnea (Respiratory frequency: 40 cycle/ min) with a rapid respiratory failure and a cardiac arrest. She died after one hour of resuscitation attempts.

Autopsy showed:

- important nonspecific signs of asphyxia (cyanosis, multivisceral congestion, sub pleural petechiae, important cerebral oedema);
- the absence of any cause of death related to the delivery (no uterus lacerations/rupture; no vaginal lacerations; no sign of acute hemorrhage; no amniotic embolism at histological examination);

Fig. 1. Gastric independent cell carcinoma with a signet-ring cell diffuse carcinoma, white arrowhead signet cell (hematoxylin and eosin A x100, B x400).

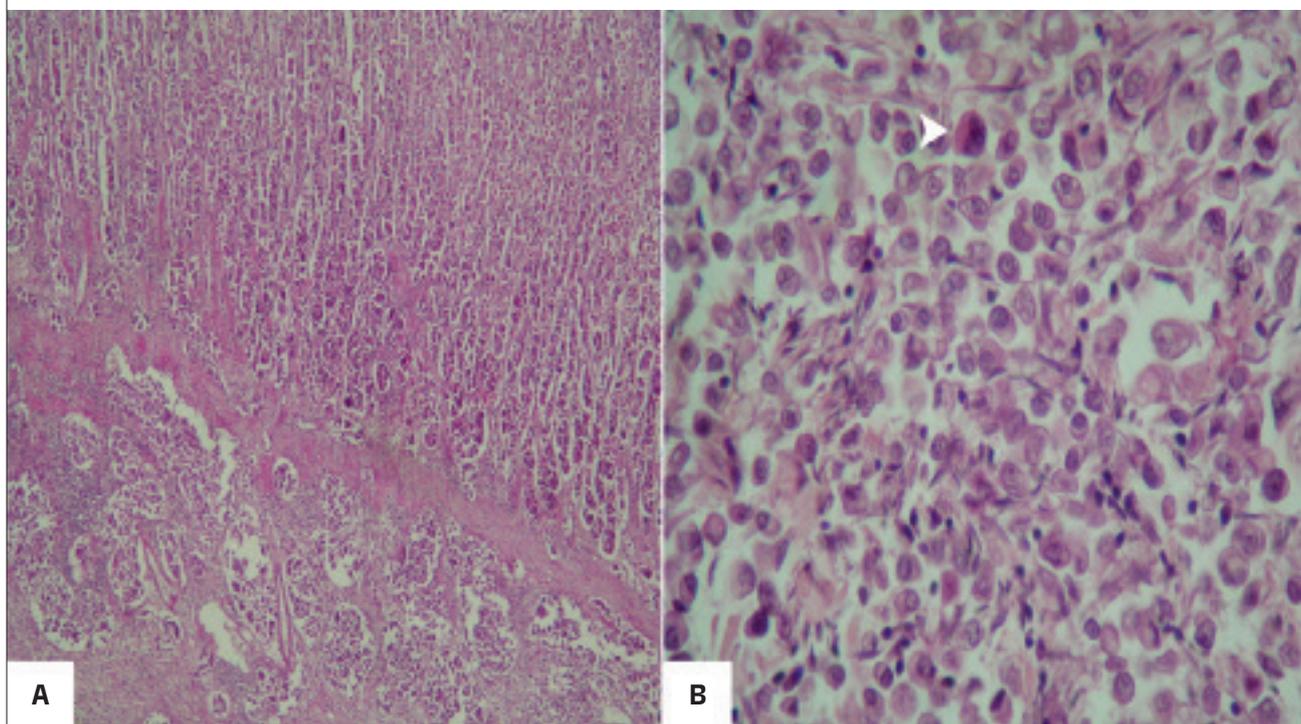
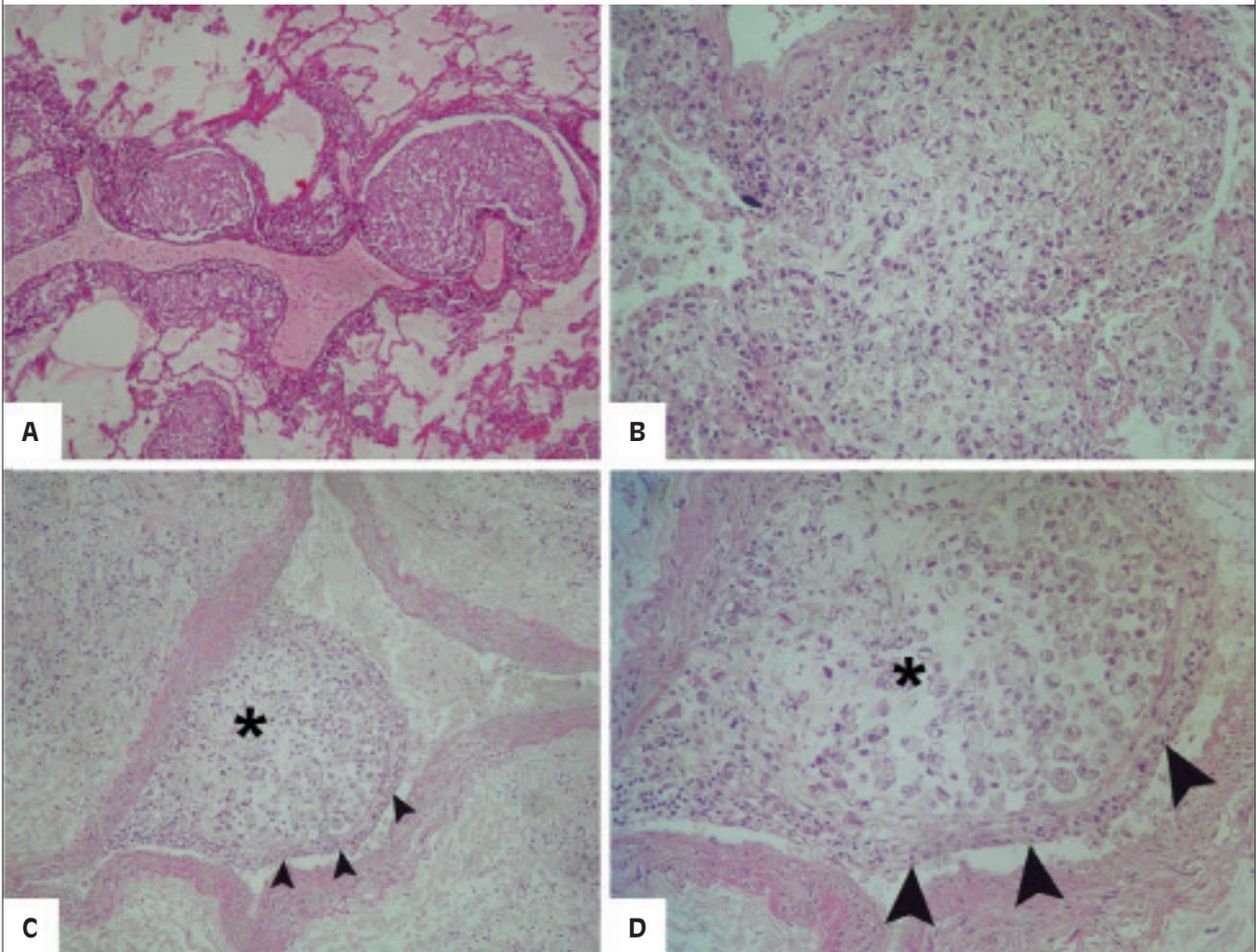


Fig. 2. A, B: an aspect of lung carcinomatosis miliary (hematoxylin and eosin A x100, B x200) C: pulmonary tumor thrombosis (*) (hematoxylin and eosin x100), D: fibrocellular and fibromuscular intimal proliferation (black arrowhead) in the lung arteries (hematoxylin and eosin x200).



- the presence of a whitish indurated 7-centimeter mass located at the big curvature of the stomach, invading the whole stomach-wall with massive direct invasion to the duodenum, pancreas and peritoneum;
- multiple whitish masses in both lungs giving the aspect of a miliary and three similar masses in the spleen measuring between 1 and 3 cm;
- multiple peri-pulmonary and aortic nodes.

Microscopic findings consisted in a primary signet ring cell carcinoma without any adenocarcinomatous component, invading the adjacent structures, such as the aortic wall, the mediastinal lymph nodes, duodenum and lungs. Pulmonary localizations caused a multiple pulmonary tumor thrombotic microangiopathy (PTTM), with neoplastic obstruction of about 90% of pulmonary small arteries and arterioles often associated with fibrocellular and fibromuscular intimal proliferation in the arteries. No amniotic emboli were observed in the lung sections. We noticed neither uterine nor vaginal rupture. Immunohistochemistry was not applied. Post mortem toxicological investigations were negative. Death was

considered to be due to an acute heart failure due to a primary gastric signet ring cell carcinoma complicated with multiple pulmonary tumor thrombotic microangiopathy (PTTM).

Discussion

Gastric cancer may be sporadic or hereditary. Sporadic form accounts for 95% of the cases. Its pathogenesis is complex with 3 major inducing factors:

- *Helicobacter Pylori* (HP) infection,
- Specific host susceptibility (genetic alterations of the inflammatory response mediation factors to HP);
- Environmental influence (especially interaction between HP and alimentation and cigarettes)²⁻¹³.

The two cases reported did not show dyspeptic signs that could reveal an HP infection or early signs of gastric carcinoma. Microscopic findings didn't show an inflammatory gastritis secondary to HP infection. While interviewing respectively the father and the husband of our

two patients, no familial history of malignancy was recorded. Yet, we don't know if there are any cases of HP infection in the family.

Our observations are interesting because they involve young patients. This wasn't the case in many studies in the literature. Among 48 patients with gastric carcinoma with PTTM, Chinen et al.⁷ reported a mean age of 52,4 years-old with only 4 cases under 30 years (11, 17, 24 and 29 years-old).

PTTM causes severe clinical manifestations. The main symptom is dyspnea¹⁻¹¹ as shown in our observations. However other symptoms such as cough, chest pain, abdominal pain, could be related to cor pulmonale¹². PTTM can be revealed by pulmonary hypertension, right side heart failure or even sudden death¹².

In PTTM, pulmonary hypertension is considered to be simultaneously due to direct vascular obstruction and to a remodeling of the arterial wall secondary to the interaction with tumor cells⁸⁻¹². Pulmonary hypertension and cor pulmonale are known as lethal complications of PTTM, with death occurring in a short period after presenting PTTM related symptoms⁷. Srigley and Pollanen⁹ reported four cases to highlight the importance of searching pulmonary hypertension evidence at autopsy especially in patients presenting gastric carcinoma. Our first observation showed an unexplained right ventricle dilatation at autopsy. According to the microscopic findings, we diagnosed cor pulmonale due to the PTTM.

In conclusion, PTTM is a rare but known lethal complication of gastric carcinoma. In the cases of sudden death in which a gastric carcinoma is observed, It could be helpful to look for evidences of cor pulmonale especially a right ventricle dilatation or hypertrophy, sometimes with edema of the legs and to perform histological observation of the lungs to look for a PTTM.

References

- Schmidt N, Peitz U, Lippert H, et al. *Missing gastric cancer in dyspepsia*. Aliment Pharmacol Ther 2005;21:813-20.
- Bornschein J, Malfertheiner P. *Gastric carcinogenesis*. Langenbecks Arch Surg 2011;396:729-42.
- Ru G-QQ, Wang H-JJ, Xu W-JJ, et al. *Upregulation of Twist in gastric carcinoma associated with tumor invasion and poor prognosis*. Pathol Oncol Res 2011;17:341-7.
- Corral JE, Delgado Hurtado JJ, Domínguez RL, et al. *The descriptive epidemiology of gastric cancer in Central America and comparison with United States Hispanic populations*. J Gastrointest Cancer 2015;46:21-8.
- Roder D. *The epidemiology of gastric cancer*. Gastric Cancer 2002;5:5-11.
- Chinen K, Kurosumi M, Ohkura Y, et al. *Sudden unexpected death in patients with malignancy: a clinicopathologic study of 28 autopsy cases*. Pathol Res Pract 2006;202:869-75.
- Chinen K, Tokuda Y, Fujiwara M, et al. *Pulmonary tumor thrombotic microangiopathy in patients with gastric carcinoma: an analysis of 6 autopsy cases and review of the literature*. Pathol Res Pract 2010;206:682-9.
- Corradi D, Mormandi F, Tanzi G, et al. *Fatal cor pulmonale caused by pulmonary tumor microembolism in a patient with occult gastric cancer*. Cardiovasc Pathol 2006;15:157-60.
- Srigley JA, Pollanen MS. *Sudden death with clinically undiagnosed pulmonary hypertension*. J Clin Forensic Med 2005;12:264-7.
- Herbay A von, Illes A, Waldherr R, et al. *Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension*. Cancer 1990;66:587-92.
- Uruga H, Fujii T, Kurosaki A, et al. *Pulmonary tumor thrombotic microangiopathy: a clinical analysis of 30 autopsy cases*. Intern Med 2013;52:1317-23.
- Roberts KE, Hamele-Bena D, Saqi A, et al. *Pulmonary tumor embolism: a review of the literature*. Am J Med 2003;115:228-32.
- Barber M, Fitzgerald RC, Caldas C. *Familial gastric cancer - aetiology and pathogenesis*. Best Pract Res Clin Gastroenterol 2006;20:721-34.