Caso Clínico
Case Report

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Estômago em melancia, pericardite hemorrágica, tumor de pequenas células do pulmão e carcinoma pavimento-celular síncrono da base da língua

Watermelon stomach, hemorrhagic pericarditis, small cell carcinoma of the lung and synchronous squamous cell carcinoma of the tongue base

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Resumo

Baseados num caso de gastropatia antral com ectasia vascular (estômago em melancia) associado a pericardite hemorrágica e a um carcinoma de pequenas células do pulmão com metástases ganglionares ao longo do mediastino e a um carcinoma pavimentocelular síncrono da base da língua, os autores fazem uma revisão dos aspectos clínicos, endoscópicos e histopatológicos deste tipo de gastropatia, da sua associação a outras doenças e das possibilidades terapêuticas actuais por via endoscópica. Referem-se igualmente as causas mais frequentes de pericardite hemorrágica, salientando-se a

Abstract

Based on a case of gastric antral vascular ectasia (watermelon stomach) that was associated with hemorrhagic pericarditis, small cell lung carcinoma with mediastinal lymph node metastases and a synchronous squamous cell carcinoma of the base of the tongue, the authors made a review of the clinical, endoscopic and histopathological aspects of this type of gastropathy, and its association with other diseases, and of the results of its endoscopic therapy. The causes of hemorrhagic pericarditis are considered, emphasizing the necessity to know if the effusion has

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necessidade de esclarecer se o derrame é ou não de origem neoplásica. Não está referida na literatura a associação deste tipo de gastropatia ao carcinoma de pequenas células do pulmão nem ao carcinoma pavimento-celular da base da língua. A invasão extensa dos gânglios mediastínicos pelo carcinoma de pequenas células do pulmão é ocorrência frequente.

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Palavras-chave: Gastropatia antral com ectasia vascular, estômago em melancia, carcinoma de pequenas células do pulmão, carcinoma pavimentocelular da base da língua, pericardite hemorrágica.

a malignant etiology. To the best of our knowledge the association of watermelon stomach to small cell lung carcinoma and squamous cell carcinoma of the base of the tongue has not yet been described. Extensive metastases to mediastal lymph nodes are common to small cell lung carcinoma.

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Key-words: Gastric antral vascular ectasia, watermelon stomach, small cell lung carcinoma, oat cell lung carcinoma, squamous cell carcinoma of the base of the tongue, hemorrhagic pericarditis.

Introduction

Watermelon stomach is a characteristic endoscopic finding of Gastric Antral Vascular Ectasia (GAVE), so named because of the intensely erythematous longitudinal streaks or columns of ectatic and sacculated blood vessels at the apices of prominent folds running across the gastric antrum and radiating to the pylorus sphincter, and resembling strips on a watermelon rind[1,2]. GAVE is different from ordinary antral gastritis by its location on the antral folds and sharply demarcated lesion that blanches on pressure[3].

GAVE is a rare cause of chronic iron deficiency anaemia due to slow and intermittent gastrointestinal bleeding, brought about by the erosion of submucosal ectatic vessels through the gastric mucosa[4]. Since the diagnosis is often delayed, it is common for patients to have received multiple packed red cell transfusions[5]. Even though it is a rare disorder, GAVE is responsible for roughly 4% of non-variceal upper gastrointestinal bleeding[6]. Profuse gastric hemorrhage is rare with this disorder but may occur as a result of superimposed bleeding diathesis which is present in the majority of patients reporting melena, and is determined by the concomitant presence of conditions such as biliary cirrhosis, valvular heart disease, congestive heart failure, non-steroidal anti-inflammatory use, CREST syndrome and systemic sclerosis, and chronic renal insufficiency, which can occur in association with watermelon stomach[3]. Most cases of GAVE are idiopathic and occur more commonly in older women (with a 9:1 female-to-male ratio). Achlorydria is a frequent finding in these patients due to atrophic gastritis[7]. Rarely, GAVE may occur in association with bone marrow transplantation[8], pernicious anemia[9], diabetes[10], chronic obstructive pulmonary disease[10],

lymphoma[11], glucagonoma[12], and neuroendocrine tumor (gastric carcinoid)[10].

The association of GAVE with cirrhosis and portal hypertension is considered unreliable with regards to a cause and effect relationship[13]. It is important to differentiate GAVE from portal gastropathy because the former responds to endoscopic therapy but not to portal hypertension reduction, whereas the latter does not respond to endoscopic therapy but responds to portal pressure reduction[13].

The authors present a case of a 59-year-old woman with a previous history of chronic anemia, who was admitted due to acute dyspnea and with an initial diagnosis of hypoxemic bronchopneumonia. The investigation of the patient concludes for the association of GAVE to: (1) Small Cell Lung Carcinoma (SCLC) with mediastinal lymph node metastases, (2) a synchronous Squamous Cell Carcinoma of the base of the tongue, and (3) malignant hemorrhagic pericarditis.

Clinical report

A 59-year-old Caucasian female was admitted to our Unit on 08AUG21 due to progressive dyspnea with a provisory diagnoses of Acute Bronchopneumonia, Congestive Heart Failure and Iron Deficiency Anemia. She was started on Ceftriaxone and Chlarytromycin.

The patient started feeling sick a month prior to admission (PTA), when she became anorexic and asthenic. Fifteen days PTA, the patient developed cough productive of mucopurulent sputum. Ten days PTA, she began to complain of odynophagia and dysphagia for solid food, as well as progressive orthopnea. There was also associated 10 kg weight loss. She denied any other symptoms. Past medical history revealed she had been treated for pulmonary tuberculosis (20 years ago) and gastric ulcer. She was also frequently noted to be anemic. She has been a heavy smoker (40 cigarettes/day) and a heavy alcoholic drinker (but has stopped 12 years ago).

On **physical exam** she was pale, very thin, profoundly dehydrated, and in respiratory distress with a RR=30 breaths/min, BP=87/68 mm Hg, HR=97 beats/min, T^0=35.5ºC. and supraclavicular retraction, blood pressure 87/68 mm Hg, heart rate 97 bpm, temperature 35.5ºC. She was edentulous and had frequent sialorrhoea. There was supraclavicular retraction and numerous supraclavicular lymphadenopathies. Thyroid gland was unenlarged. Auscultation of the lungs revealed bilateral diffuse ronchi and wheezes. Heart sounds were slightly muffled. Negative for breast masses, hepatosplenomegaly and peripheral edema.

Blood tests showed the following findings: leukocytosis with neutrophilia (18 600/mm^3; 94.3%); microcytic anemia (Hb 7.5 g/dL; MCV 76.4 fl; MCH 24.2 pg), adequate platelets. Normal protime, elevated PCR 16.4 mg/dL (N<1.00); hypoalbuminemia 2.62 g/dL; low serum iron and transferrin and ferritin; no monoclonal gammapathy; elevated LDH 752 U/L (N 313-618); other biochemical analysis were normal (glucose; renal and liver function tests; lipid profile; calcium and phosphorus); normal thyroid function tests; Arterial Blood Gas: respiratory alkalosis and hypoxemia (pH 7.514; pCO_2 – 32.7 mmHg; pO_2 – 53.1 mmHg; HCO^{3-} mmol/L; Sat O_2 – 90.2%); several **blood cultures**, including **BACTEC**, were negative. **Sputum exam**: Ziehl-Nielsen and Lowenstein were negative. The **Chest**

PA revealed an enlarged cardiac silhouette, a widened superior mediastinum and an ill-defined image of right paracardiac condensation (Fig. 1A). A comparative reading with a chest x-ray dated Dec 2006 (Fig. 1B) lead us to suspect pericardium effusion, which was confirmed by **echocardiography**, showing massive effusion and signs of cardiac pre-tamponade, with diastolic collapse of the right atria and pre-collapse of the right ventricle (Fig. 1C), and estimated PSAP of 51 mm Hg. An immediate **pericardiocentesis** was performed with drainage of 820 mL of pericardial hemorrhagic effusion (in two days) that yielded moderately elevated number of granulocytes and erythrocytes, but negative for *Mycobacteria* and other bacteria on culture. No malignant cells found. **Upper gastrointestinal endoscopy to explain dysphagia** showed a normal esophagus, but revealed typical aspects of GAVE (Fig. 2). We were unable to confirm it histologically through biopsy, because the patient became very dyspneic during the procedure. Bronchofibroscopy was not possible to realize due to progressive respiratory failure and the impossibility to do it in our hospital. **Biopsy of a supraclavicular lymph node** showed infiltration by small cell carcinoma (CAM 5.2 +, AE1/AE3 +, CK7 +; sinaptophysin +, LCA -, TTF1 , cromogranin -; S100 -). The patient's condition rapidly deteriorated with development of acute pulmonary edema. After stabilizing the patient, a **non-contrast thoracic CT scan** (Fig. 3) was done, which revealed prominence of the central pulmonary artery and main right and left branches; numerous hypertrophied mediastinal lymphadenopathies, mainly in the peri-esophageal area, causing compression of the medium esophagus and also of the main right

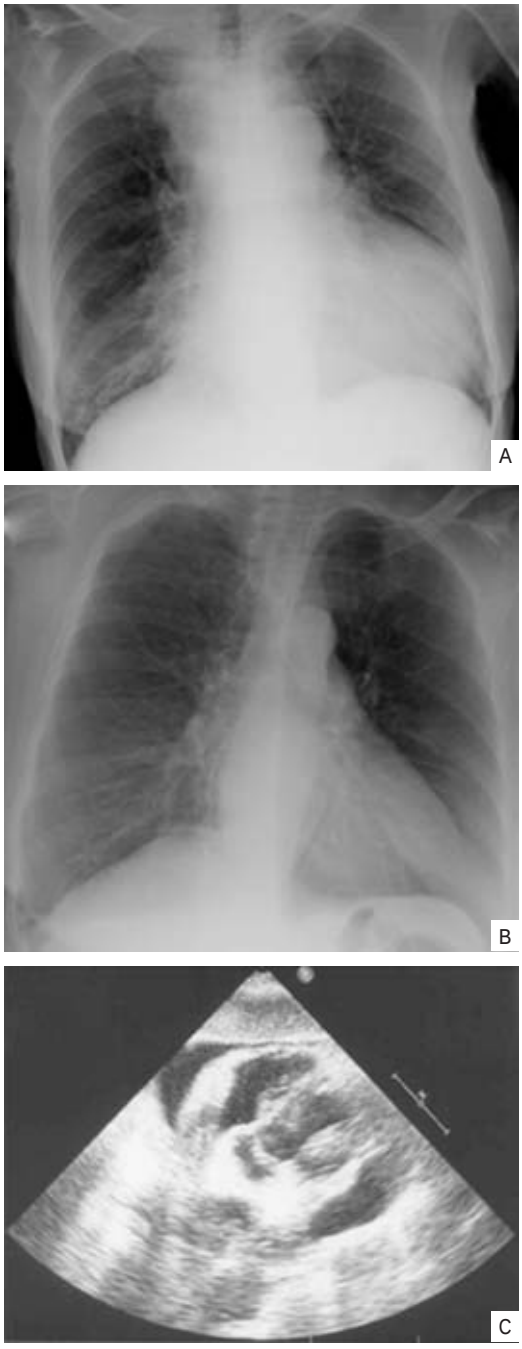

Fig. 1 – A/B: PA views of the thorax X-rays (AUG08/DEC06) revealing significant enlarged cardiac silhouette; C: Echocardiography: cardiac pre-tamponade due to voluminous anterior and posterior pericardial effusion

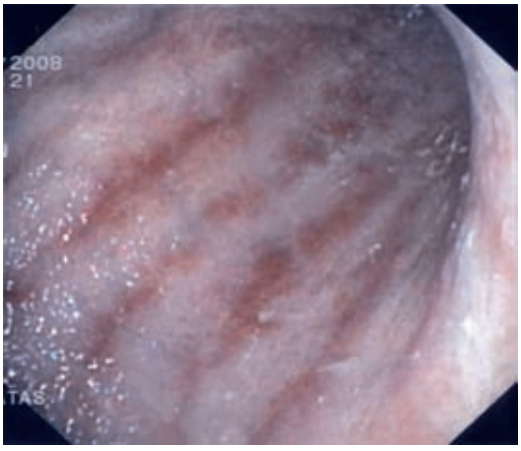

Fig. 2 – Upper gastrointestinal endoscopy showing characteristic aspects of watermelon stomach

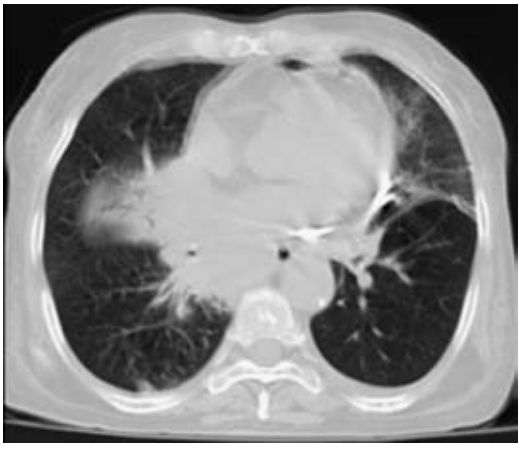

Fig. 3 – Thoracic CT-scan: numerous mediastinic lymphadenopathies causing compression of the medial esophagus and of the main right bronchus

and left bronchus. At the level of right middle lobe and of the lingual lobe there were images suggestive of infection. The patient died on the 7th hospital day (08AUG28) due to respiratory failure. There were no medical conditions to proceed to bronchofibroscopy. **Necropsy** revealed the following **macroscopic** and **microscopic** (hematoxylin-eosin) aspects (Figs. 4 A,B,C; 5 A,B,C; 6 A,B,C; 7 A,B,C): **Macroscopically**: a) an ulcerated tumor of the base of the tongue measuring 3.5 cm at its widest diameter; b) a mediastinal tumor mass comprising a lymphadenopathic conglomerate involving all the compartments and the right pulmonary hilus, the main right bronchus and a small adjacent area of the lung; c) a tumor metastasis on the right adrenal; d) a tumor metastasis on the right kidney; e) a tumor metastasis on the spleen; **Microscopically**: a small cell carcinoma (identical to the one described on the ganglionar biopsy) of the right bronchus with extensive mediastinal, tracheal and ganglionar extension, and with metastasis to the spleen, right adrenal, right kidney, pericardium, and hypophysis. Small cell carcinoma was confirmed by neuroendocrine markers using immunohistochemis-

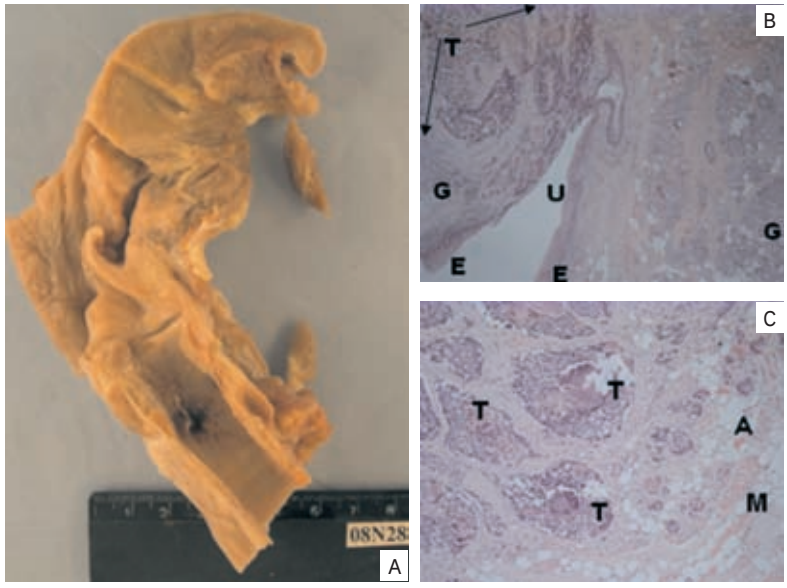

Fig. 4 – A: Base of the tongue with an extensive ulcerated lesion, with macroscopic extension to the valecula; B: HE 10X5 – Squamous neoplasia (T) infiltrating the muscle of the tongue and the minor salivary glands (G), ulcerating (U) the squamous epithelium (E); C: HE 10X10 – Squamous cell carcinoma (T) proliferating and infiltrating the neighbour tissues, adipose tissue (A), muscle (M).

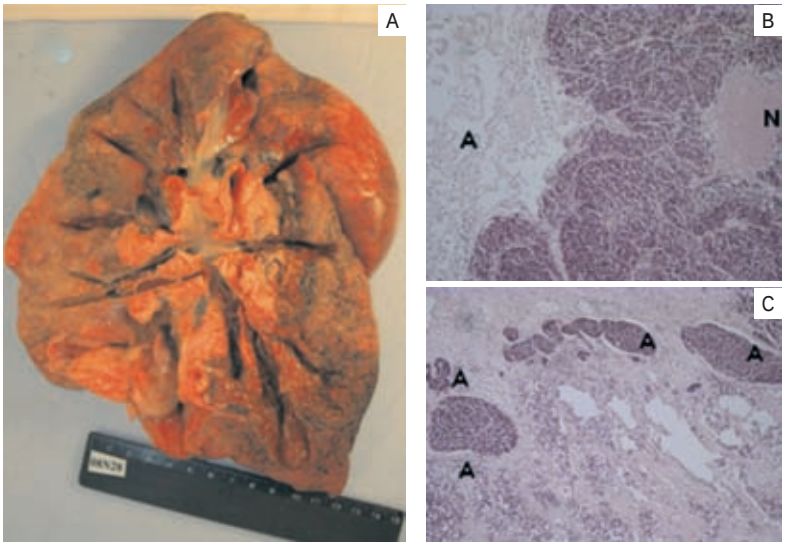

Fig. 5 – A: Right lung with a tumor mass proliferating within the submucosa of the main bronchus and infiltrating the hilus. The mucosal surface of the bronchial tree was intact; B: HE 10X10 – SCLC with necrosis (N); C: HE 10X10 – Lymphatic invasion by the SCLC (A)

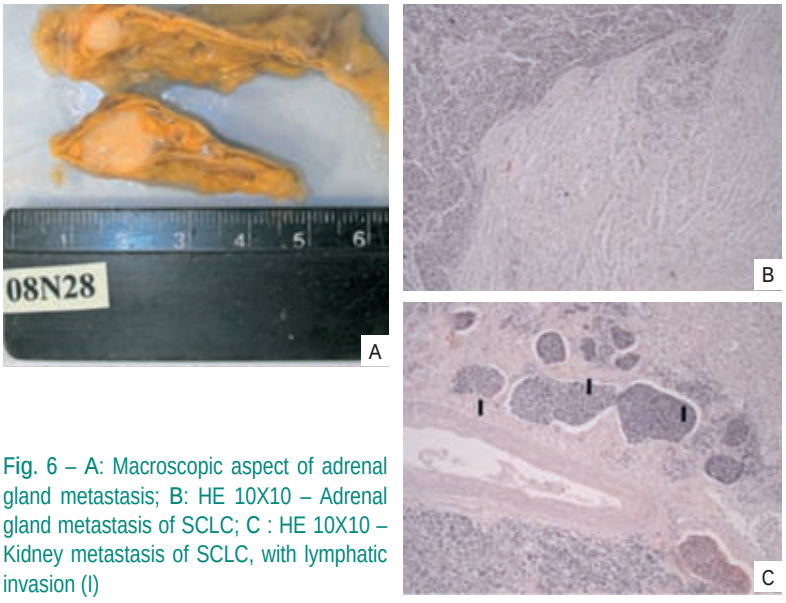

Fig. 6 – A: Macroscopic aspect of adrenal gland metastasis; B: HE 10X10 – Adrenal gland metastasis of SCLC; C : HE 10X10 – Kidney metastasis of SCLC, with lymphatic invasion (I)

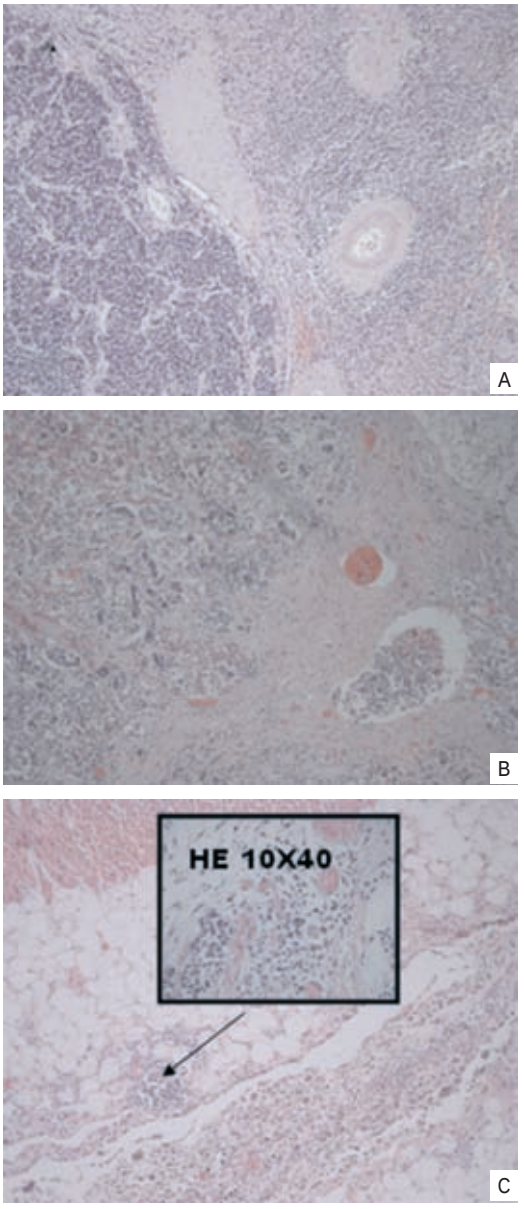

Fig. 7 – A: HE 10X10 – Spleen metastasis of SCLC; B: HE 10X10 – Hypophysis gland metastasis of SCLC and squamous cell carcinoma; C: HE 10X10 – Pericardium metastasis of SCLC

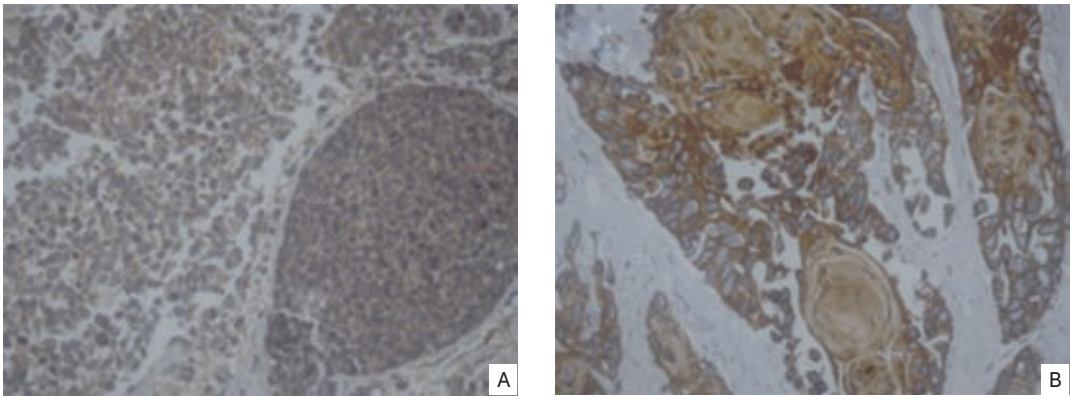

Fig. 8 – Immunohistochemistry: A: 10X40 – SCLC expressing neuroendocrine markers (cromogranin, NSE, and sinaptophysin); B: 10X40 – The neoplasia that involved the hypopharynx, expressed positivity for cytokeratins (34BE12 or CK903)

try (Fig. 8A). Surprisingly, the tumor located at the tongue base was a (synchronous) squamous cell carcinoma with metastasis only in the hypophysis, which was confirmed by immunohistochemistry (Fig. 8B). There were areas with poorly differentiated pattern but the neuroendocrine markers (sinaptophysin, cromogranin, NSE) were consistently negative. The ultrastructural study performed on both tumors (bronchus and tongue) by electron microscopy confirmed the aforementioned different nature of these tumors (Fig. 9).

Discussion

The findings of a prominent antral folds and antral thickening in upper gastrointestinal radiologic series and on CT scans in an elderly patient with chronic anemia should alert the radiologist to the possibility of GAVE, which should be confirmed endoscopically with biopsy[14].

GAVE can be safely biopsied with only minimally increased and minor bleeding because of its low-intravascular pressure. Biopsy of the involved gastric folds reveals characteristic findings of dilated, tortuous mucosal capillaries often occluded by bland fibrin thrombi in the lamina propria and dilated submucosal veins without inflammatory infiltration[15,16], together with foveolar

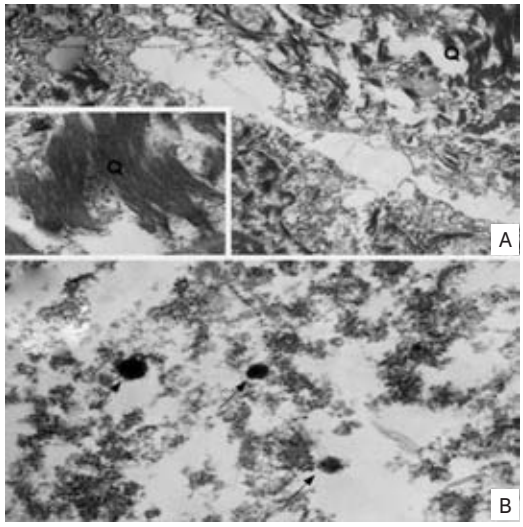

Fig. 9 – Post-mortem samples recovered from paraffin blocks and reprocessed for electron microscopy: A: Tumor of the base of the tongue. The cytoplasm of the tumor cells displays well developed bundles of keratin filaments (Q). Inset – High magnification of keratin filament; B: Mediastinic tumor. Dense neurosecretory-like granules (arrows) in the cytoplasm of the tumor cells

hyperplasia and fibromuscular spindle cell hyperplasia of the lamina propria[17].

The cause of GAVE is unknown, but Jabbari[1] had proposed that it could result from repetitive low-grade trauma caused by repeated prolapse of the loosely attached mucosa of the distal antrum into the duodenum during gastric peristalsis due to antral hypercontractility, primary or acquired, with consequent elongation and secondary reactive muscular hyperplasia and ectasia of the mucosal vessels. Thrombosed ectatic vessels are a distinctive feature and are seen only in GAVE[18,19].

Since GAVE is not acid related pharmacotherapy with histamine receptor antagonists and proton pump inhibitors is ineffective. Evidence for effective pharmacologic therapy with oestrogen (and/or progesterone), tranexamic acid or thalidomide, are mentioned in some case reports only[6]. Ultimately, treatment of any underlying medical comorbidities may lead to resolution of GAVE[6].

Many authors consider endoscopic therapy as the primary therapy, namely argon plasma coagulation (APC), which appears to be preferable in comparison with contact methods (heater probe, electrocautery with bipolar electrocoagulation probe, or Gold probe) or other noncontact ablative modality (Nd:YAG laser). Despite some contrary opinion[10], APC should probably be the treatment of choice for GAVE due to the diffuse nature and superficial location of the lesion[20,21]. APC is well tolerated and safe because it produces only shallow tissue injury[22]. Usually several sessions are needed, but requirements of blood transfusions are generally diminished in the large majority of patients[23,24,25].

Antrectomy is recommended if endoscopic hemostasis fails. It removes the lesion and nearly always cures the disease, but entails significant morbidity and 5% mortality[26].

Despite the generally good results obtained with APC, recently there were some authors who were able to get a much better result with Endoscopic Band Ligation (EBL) in cases of GAVE (especially in patients having large areas of diseased mucosa and submucosa)[27] that have been treated with APC but would still have recurrent hemorrhage[27]. These authors suggest that EBL could be more superior to endoscopic thermal therapy (ETT) for the management of GAVE. In their study consisting of 22 patients treated either with EBL or ETT, including four patients in the EBL group that failed prior ETT, they found that statistically EBL had a significantly higher rate of bleeding cessation (67% vs 23%, P = .04), fewer treatment sessions required for cessation of bleeding (1.9 vs 4.7, P = .05), a greater increase in hemoglobin values (2.8 g/dL vs 0.9 g/dL, P = .05), a greater decrease in transfusion requirements (-12.7 vs -5.2, P = .02), and a greater decrease in hospital admissions (-2.6 vs -0.5, P = .02) during the follow-up period. EBL for GAVE includes ligation bands applied to abnormal-appearing mucosa in the antrum, beginning in the most distal antrum, adjacent to the pylorus, and subsequently more proximally until as much as possible of the abnormal-appearing mucosa, thus obtaining resection of large amounts of antral mucosa and submucosa. The superiority of EBL compared with ETT is probably due to the fact that EBL providing more reliable obliteration of the abnormal vasculature in the mucosa and submucosa. Complications are also rarer with EBL than with APC[27].

The main causes of non-traumatic hemorrhagic pericarditis are tuberculosis in deve-

loping countries, frequently associated today with AIDS[28], and malignancy in developed[29]. Meyers *et al*[30] demonstrated that most pericardial effusions are sero-sanguineous or hemorrhagic (72.6%), there was a great number of possible etiologies, and erythrocytes counts were not significantly different among the diagnostic groups. Other possible causes are post-myocardial infarction rupture of the free wall of the ventricle, retrograde bleeding due to dissecting aneurysm of the proximal thoracic aorta (mostly due to atherosclerotic disease; on old times also syphilitic aneurysm), anticoagulant or antifibrinolytic therapy, congestive heart failure, uremia, connective tissue diseases, and any type of infectious pericarditis[31,32,33,34,35,36,37,38,39].

In a review of 127 patients with malignancy-related pericardial effusion by Wilkes[40], 55% of cases were malignant in etiology while in the remaining 45%, a malignant cause for the effusion could not be determined and no definitive etiology was identified in 74% of these effusions. Diagnosis by cytology and pericardial biopsy had sensitivities of 90% and 50%, respectively. 71% of primary tumors were adenocarcinomas of the lung, breast, esophagus, hematologic malignancies, and of unknown primary site.

Effusions caused by tumors often progress to cardiac tamponade, eliciting bleeding in the pericardium[41,42]. Malignancy-related hemorrhagic pericardial effusions are frequently a terminal event in patients with disease unresponsive to therapy. However, bloody pericardial effusion can be the presenting manifestation of a newly diagnosed malignancy, either metastatic[43,44,45,46,47], or rarely due to primary malignancy of the pericardium (exº mesothelioma[48]). We shell also think on the possibility of pericardial effusion due to primary malignancy of the heart, and on Kaposi sarcoma and lymphoma in patients with AIDS[48].

In most cancer patients with pericardial effusion, or tamponade, it is important that neoplastic involvement of the pericardium be confirmed by identification of malignant cells in pericardial fluid. Confirmation is important because other forms of pericardial disease can occur in patients who have or had cancer[48,49,50].

In our patient the cytological examination of the pericardium fluid was negative, but the extensive histological analysis of the pericardium during necropsy, revealed a tiny metastatic focus of small cell carcinoma, confirming the clinical suspicion of a malignant etiology of the pericardium effusion.

The median age at diagnosis for primary cancer of the tongue is 61 years of age. The lifetime risk of developing cancer of the tongue is 1 in 361 men and woman[51]. People who drink large amounts of alcohol and use tobacco are especially at risk. Tongue cancers are subdivided in cancers of the proximal two-thirds of the tongue – buccal tumors, and cancers of the posterior third – tongue base cancers or oropharyngeal cancers, which are often diagnosed quite late. Most of the tumors are squamous cells tumors[52].

Symptoms of cancer of the tongue are: (a) chronic pain in the pharynx, mostly at mastication or swallowing, (b) numbness of the tongue or of the mouth, (c) a small lump, (d) unexplained bleeding from the tongue[53], (e) non-cicatrizing ulcer of the tongue, (f) otalgia due to pain irradiation, (g) bad breath, (h) drooling, (i) difficulty in breath-

ing, (j) trouble swallowing, (k) difficulty in speaking, (l) bad odour breath. If untreated, the tumor may spread throughout the tongue to the floor of the mouth and to the gum (jaws). As tumor grows it can evolutes to cause metastases to lymph nodes in the neck and later on in the rest of the body[54].

Neuroendocrine carcinomas are tumors and are more commonly found in the thyroid, lung and skin. Their diagnosis is based on the recognition of the characteristic morphology and architecture, but immunohistochemical confirmation of the neuroendocrine nature of neoplasm cells is always required.

In our patient, the problem wasn't centered on the histological diagnosis but rather at his origin. The main tumor mass was located at the mediastinum, but is starting to invade the bronchus and lung. We could speculate a thymus origin, but small cell carcinoma is rare at the thymus, and it is much more frequent at the lung. In order to make a diagnosis of small cell carcinoma of the thymus, it is necessary to exclude a lung origin, which we certainly can't do in our case. So, we think that we have to consider that in this patient, the origin was pulmonary with extensive mediastinal and ganglionar extension.

SCLC has an aggressive behavior, with rapid growth, early spread to distant sites (mediastinal lymph nodes, liver, bones, adrenal glands, and brain), frequently exhibit paraneoplasm syndromes and neurologic autoimmune phenomena, and distinct sensitivity to chemotherapy and radiotherapy. Surgery is rarely useful. SCLC generally presents with onset of symptoms within 8-12 weeks prior to admission. The symptoms can result from local tumor growth, intrathoracic spread, distant spread, para-neoplasm syndromes (inappropriate secretion of antidiuretic hormone, ectopic secretion of ACTH) and autoimmune neurologic phenomena. Common symptoms are fatigue, anorexia, weight loss, cough, dyspnea, hemoptysis, symptoms due to vena cava obstruction, hoarseness, dysphagia, stridor, neurological dysfunction, bone pain, abdominal pain due to metastases. Usually SCLC is centrally located and may cause obstruction of the major airway, with distal collapse and post-obstructive pneumonitis. Due to rapid growth and spread, patients at presentation may have a very large intra-thoracic tumor, making difficult to distinguish primary tumor from lymph node metastases. Pleural and pericardial effusions are common[55].

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