

Letters to the Editor

Pulmonary Haemorrhage and Haemothorax After Massive Ingestion of Clopidogrel as a Suicide Attempt

Hemorragia pulmonar y hemotórax tras ingesta masiva de clopidogrel con fines autolíticos

To the Editor:

Clopidogrel is an oral antiplatelet agent derived from thienopyridine; it inhibits platelet aggregation induced by adenosine diphosphate (ADP). At usual doses, of up to 600mg, pulmonary haemorrhage and haemothorax are exceptional, when treating acute myocardial infarction (AMI), ischaemic cerebrovascular events and when performing angioplasty.¹⁻⁴ Little information is available about complications after ingesting higher doses. We had the opportunity of assisting a female patient that, after a suicide attempt with a single Clopidogrel dose of 1,875mg, developed pulmonary haemorrhage and haemothorax that were resolved by conservative management.

This 49-year-old woman had suffered a cerebrovascular stroke the previous year and since then was on Plavix® (Clopidogrel), 75mg/day, and acetylsalicylic acid (100mg/day). When she was admitted 36 hrs after ingesting 25 capsules of Clopidogrel (1,875mg), she was afebrile, sleepy, and without wounds or bruises. Arterial pressure was 150/95mmHg, heart rate 101bpm and respiratory rate 22 breaths/min. In the lab tests, haemogram showed haemoglobin 10.4g/dl, haematocrit 31%, mean corpuscular volume (MCV) 72.2fl, mean corpuscular haemoglobin (MCH) 24.2pg/ml, mean corpuscular haemoglobin concentration (MCHC) 335g/l, and red cell distribution width (RDW) 17.4%. In the coagulation study, activated partial thromboplastin time (APTT) was 23 s and fibrinogen 627mg/dl, and all other values were normal. Blood biochemistry parameters were: aspartate aminotransferase 380U/l, alanine aminotransferase (ALT) 320U/l, Lactate Dehydrogenase (LDH) 333U/l, creatine kinase (CK) 13.842U/l, myoglobin 2,128ng/ml, creatine kinase MB (mass) 167ng/ml, and serum iron 24µg/dl; with normal renal function, ions, cardiac enzymes, transferrin, and ferritin. Standard and urine sediment showed microhaematuria with 150 RBC/field and 30-100 white blood cells/field. Arterial gas analysis breathing normally (inhaling oxygen fraction: 21%) showed: pH of 7.46, arterial pressure of carbon dioxide of 33mmHg, arterial pressure of oxygen of 65mmHg, and bicarbonate of 24mEq/l. ECG showed no alterations, and thorax computed tomography showed patchy bilateral infiltrates and right pleural effusion. At day 4 a totality of 200ml of haematic pleural fluid with characteristics of haemothorax was aspirated. Induced sputum cytology showed presence of macrophages, 40% of which contained haemosiderin pigment. No neutrophilia, food or foreign bodies appeared to suggest pneumonia by aspiration (Figure). At day 11 the patient was discharged after disappearance of infiltrates, progressive normalisation of altered analytical parameters, and no further need of transfusions.

Inhibition to platelet aggregation after ingestion of Clopidogrel was observed after 2 hours, whereas repeated 75mg/day doses reach a

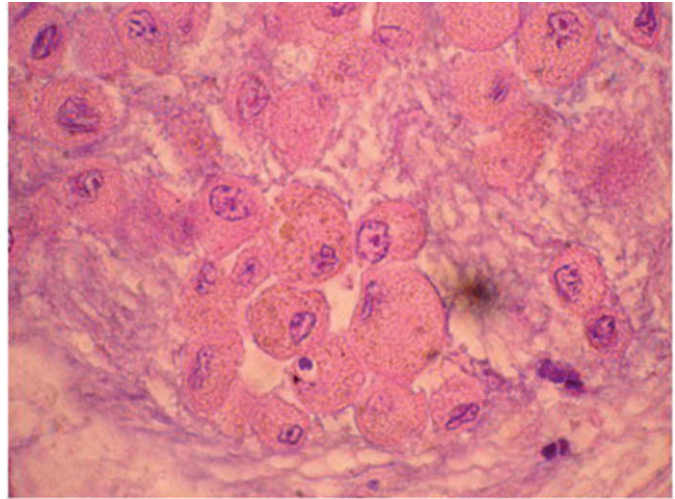


Figure. Induced sputum cytology.

maximum inhibition after 3-7 days, returning to baseline values 5 days after discontinuing treatment. At recommended doses pulmonary haemorrhage and/or haemothorax is exceptional, and their appearance is related to performance of invasive manoeuvres such as angioplasty² and with co-occurring anti-aggregating treatments such as ASA.^{3,4}

Information about overdose in humans is limited, although there are references to 2 cases of single doses —1,050mg in a 34-year-old female at a Caprie¹ study and a suicide attempt with 1,650mg in a 49-year-old male⁵— who suffered no side effects and recovered spontaneously without sequelae. In the case being discussed here, association of ASA and Clopidogrel may have favoured haemorrhage, as it had been shown by the MATCH study.⁶ This association has not shown that vascular events are reduced significantly and risk of haemorrhage increases, which is why its use should be reserved, until prospective studies being carried out are released, for those patients who have undergone relapsing vascular episodes after treatment with monotherapy.⁶ Its use in psychiatric patients with high risk of suicide attempts should be taken into consideration, although in the case of our patient and despite having had a dose much higher than those recommended, both pulmonary haemorrhage and haemothorax were resolved without sequelae.

References

- CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-39.
- Kilaru PK, Schweiger MJ, Kozman HA, Weil TR. Diffuse alveolar hemorrhage after clopidogrel use. *J Invasive Cardiol*. 2001;13:535-7.
- Gill DS, Ng K, Ng KS. Massive pulmonary haemorrhage complicating the treatment of acute coronary syndrome. *Heart*. 2004;90:e15.

4. Haro M, Álvarez LA, Baldó X, Palos A, Rubio M, Rubio M. Hemotórax bilateral secundario al tratamiento antiagregante con clopidogrel y ácido acetilsalicílico. Arch Bronconeumol. 2006;42:307-9.
5. Kocabay G, Okçular I, Acalla V, Güler K. Suicide attempt with clopidogrel. Hum Exper Toxicol. 2006;25:731-4.
6. Diener HC, Bogoulavsskyj, Bras LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. Lancet. 2004;364:331-7.

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Primary Lung Adenocarcinoma With Ovarian Metastasis: A Rare Presentation of Bronchogenic Carcinoma

Adenocarcinoma de origen pulmonar con enfermedad metastásica en ovario: una forma rara de presentación de carcinoma broncogénico

To the Editor:

Around 40% of patients with bronchogenic carcinoma have metastasis when diagnosed.¹ Although metastasis can occur in practically any organ, those most commonly affected are the bones, the liver, the adrenal glands, the brain, and the skin.¹ We describe the case of a woman with non-small cell lung cancer with metastasis to the ovary.

The patient was a 54-year-old woman with no significant medical history or history of substance abuse. She consulted the gynecology department in regard to irregular menstrual bleeding and anemia. Pelvic and transvaginal ultrasound revealed an enlarged uterus and multiple images of intramymetrial, subserous, and pedunculated nodules; 1 nodule near the abdominal cavity measured 12 cm and reached the suprapancreatic level. Given our suspicion of neoplasm, the radiology study was complemented with a computed tomography scan of the thorax, abdomen, and pelvis. This revealed massive right pleural effusion with pleural thickening and focal contrast-enhanced areas, enlarged prevascular retrocaval and paraaortic lymph nodes, and multiple blastic lesions in the dorsolumbar spine, the sacrum, and both ilea. The clinical and radiological characteristics combined to suggest an initial diagnosis of uterine tumor with extensive metastasis. A blind pleural biopsy revealed infiltration as a consequence of epithelial neoplasm, suggestive of adenocarcinoma. Following uterine dilatation to rule out malignancy, the patient underwent a full hysterectomy and double adnexectomy. The uterine tumors were leiomyomas that showed no histologic signs of malignancy. In the right ovary, immunohistochemistry revealed 1 nodular lesion with a positive thyroid transcription factor-1 (TTF-1) profile—findings consistent with metastasis from a pulmonary adenocarcinoma (Figure). The same technique applied to the pleural biopsy samples revealed tumor cells with positive TTF-1 expression. The study was concluded with a fiberoptic bronchoscopy that revealed, in the basal pyramid, an edematous mucosa with no folding causing a stenosis of the entry to the basal bronchi. The result of the bronchial biopsies was adenocarcinoma originating in the lung.

The incidence of bronchogenic carcinoma is steadily on the rise, ranking as the leading cause of tumor-related deaths in developed countries. Adenocarcinoma, which is the histologic type of cancer most frequent in women, has been showing a clear growing trend in recent years. The main factor influencing prognosis is surgical treatment, although diagnosis is usually made at advanced stages of the disease.¹ The literature contains very few cases of bronchogenic carcinoma with metastasis to the ovary, which can occur with both small cell and non-small cell carcinomas.²⁻⁵ In the case described, the form of presentation pointed to gynecological neoplastic disease with pleural metastasis as a first diagnostic possibility. Malignant pleural effusion is a frequent complication of advanced neoplastic

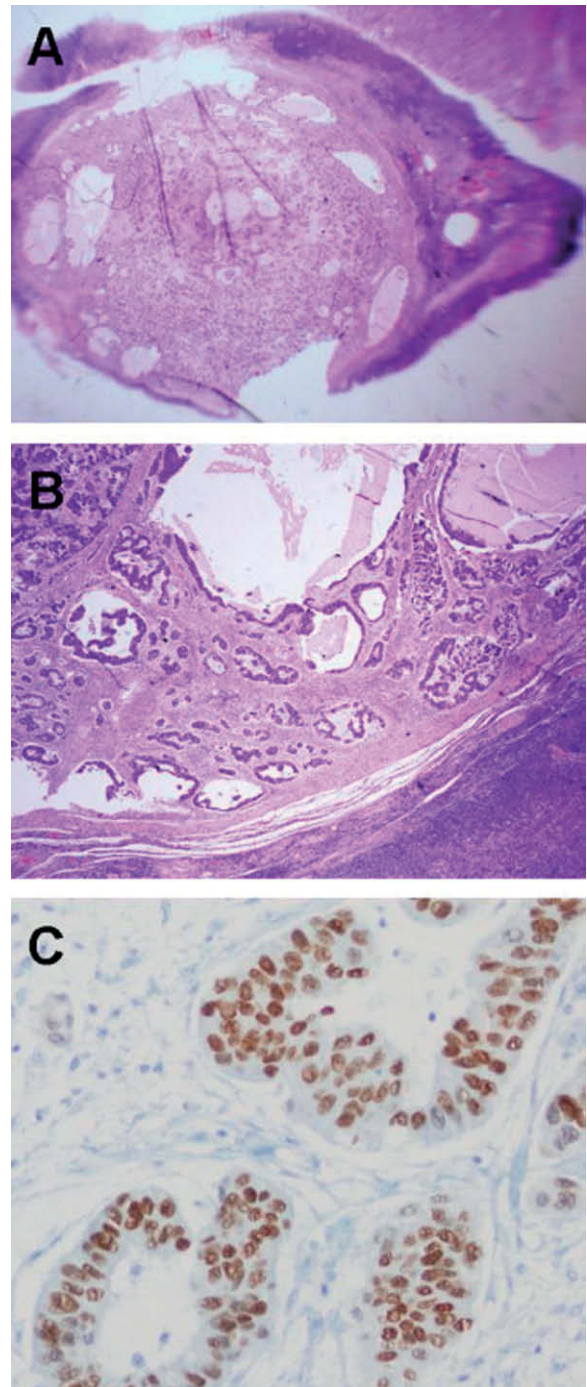


Figure. A. Macromicroscopy image of the ovarian nodule. B. Microscopy image of the ovarian tumor, clearly delimited with respect to the parenchyma of the other ovary, and with evident tubular-glandular differentiation. C. Positive nuclear immunohistochemical staining for thyroid transcription factor-1, showing a profile that was positive for keratin 7, negative for keratin 20, and negative for chromogranin.