Rare gastrointestinal metastases from primary lung cancer.
Two case reports of patients managed with emergency surgery

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BACKGROUND: *Lung cancer represents the second leading cause of death in US and the high mortality rate could be related to the diagnosis, usually, performed in an advanced metastatic stage. Gastrointestinal metastases from non-small cell lung cancer, are extremely rare and only few cases complicated by digestive haemorrhage and/or perforation have been reported in literature.*
MATERIAL AND METHODS: *We report two cases of gastrointestinal metastases and their rare clinical onset with haemorrhage and perforation of the digestive tract.*
Both patients were admitted in an emergency setting. The first case was a 59-year-old man complained of abdominal pain and massive gastrointestinal haemorrhage. An upper gastrointestinal endoscopy revealed an ulcerated gastric mass and an emergency CT-scans showed a right lung mass with biopsy conclusive for a large cell lung cancer.
The second case was a 62-year-old man with abdominal pain and shock due to gastrointestinal bleeding. He was submitted to an emergency CT-scan showing two lung nodules (1.0 and 3.5 cm of diameter) as well as widespread metastases, intraperitoneal free air and fluids.
RESULTS: *Both patients were surgical managed in emergency and pathology revealed the metastatic origin from an unknown large-cell lung cancer and a rare lung adenocarcinoma in the second one.*
CONCLUSIONS: *Despite the rare clinical condition, in patients with a diagnosis of lung cancer managed in emergency for gastrointestinal complication, gastrointestinal metastases should be taken into account, and referred to the primary disease in order to tailor the best approach.*

KEY WORDS: Gastrointestinal metastases, Lung cancer, Tailored surgery

Introduction

Cancer is the second leading cause of death in the United States and almost one-quarter of all cancer deaths are due to lung cancer (LC). A recent study by the American Cancer Society has predicted 228,820 new LC cases in 2020, with a 5-year relative survival rate still of 19% [1].

The high mortality rate could be related to the cancer stage when diagnosed; indeed, about half of patients with LC are commonly diagnosed in an advanced stage as metastatic disease [2-4].

Small cell lung cancer (SCLC) occurs with an incidence rate of 13% while non-small cell lung cancer (NSCLC) and its histological types - including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, adenosquamous carcinoma and sarcomatoid carcinoma - recur in about 84% of case [1,5-7].

The major sites of NSCLC metastases are brain (47%), bone (36%), liver (22%), adrenal glands (15%), thoracic

cavity (11%) and distant lymph nodes (10%). Any other organ metastases are very rare and overall occur only in 5% of cases[8]. Moreover, gastrointestinal metastases (GM) from LC are extremely rare with an incidence of <2% *in vivo* but, otherwise, they are quite higher (4.7-14%) in autoptic studies [9-11].

GM from LC are often diagnosed after histopathologic examination, because of complex detection until the development of acute complications (intestinal obstruction, perforation or haemorrhage) and the difficulty to distinguish unusual metastases from primary malignancies on preoperative imaging and intraoperative findings [9,12].

To the best of our knowledge, only few cases of GM from LC complicated by digestive haemorrhage and/or perforation have been reported in literature [11].

We present two cases of GM from LC resulting from two different histological types of NSCLC and their rare association with haemorrhage and perforation of the digestive tract. In the first case, metastases derived from an unknown large-cell lung carcinoma (LCLC), which is defined as a rare undifferentiated histological variant of NSCLC; while in the second case, GM derived from an unknown metastatic lung adenocarcinoma.

Case Reports

This study was performed in accordance with the Declaration of Helsinki. Written consent was obtained from patients and the study was approved by Ethics Committee of the University of Bari (protocol n. 6428, 22/07/2020).

Case N. 1

A Caucasian, 59-year-old man was admitted to our Academic Emergency Department of General Surgery with abdominal pain and massive lower gastrointestinal haemorrhage. Laboratory examinations showed marked anaemia and leucocytosis. Physical examination revealed the presence of an abdominal palpable mass. Upper gastrointestinal endoscopy showed the presence of an ulcerated tumour located in the lesser curvature of the stomach. Emergency chest and abdomen CT-scans were performed, showing a huge right lung mass measuring 15.0 cm of diameter. A biopsy of this lung mass was performed, and histopathological findings were conclusive for a LCLC. A gastric and a right colon mass infiltrating liver and abdominal wall respectively were also found. Emergency laparotomy was performed showing a very large mass involving stomach, right colon infiltrating abdominal wall, lymphadenopathy of the celiac trunk, a caseous retroperitoneal mass and peritoneal carcinomatosis (Fig. 1). A total gastrectomy *en-bloc* with a right colectomy, splenectomy, cholecystectomy and removal of
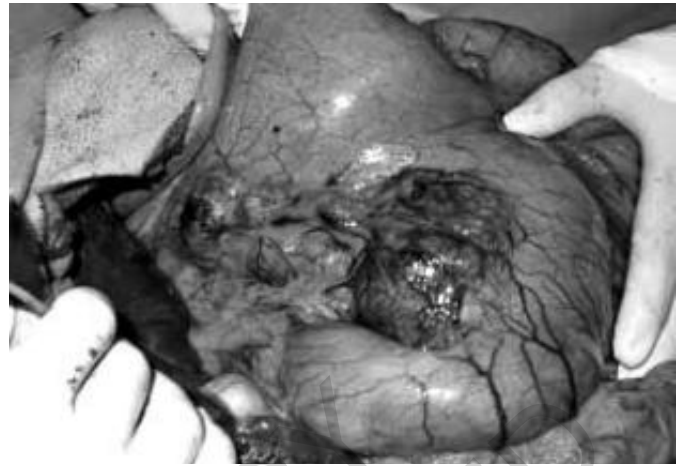

Fig. 1: Gastrointestinal metastasis from large-cell lung carcinoma. Surgical intraoperative evidence of a gastric and a right colon mass infiltrating liver and abdominal wall.
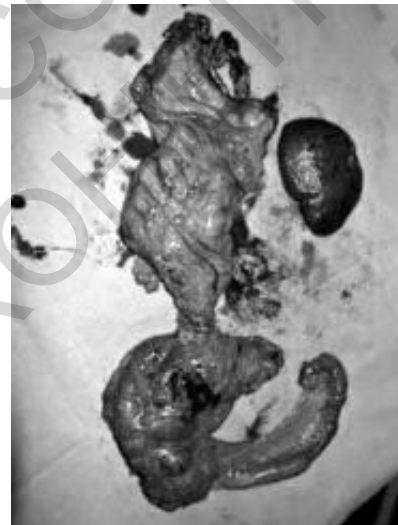

Fig. 2: Surgical management: total gastrectomy en-bloc with a right colectomy, splenectomy, cholecystectomy and removal of the retroperitoneal mass.

the retroperitoneal mass was performed (Fig. 2), followed by a Roux-en-Y with an end-to-side oesophagojejunostomy and an end-to-side ileo-transverse anastomosis. Pathology examination revealed a metastatic LCLC, involving gastric wall, adipose tissue, lymph nodes, peritoneum and, with extensive retroperitonal necrosis. Immunohistochemical analysis was positive for cytokeratin 7 (CK-7) and negative for Chromogranine A, Synaptophisin, Cytokeratin 20 (CK-20), CK-34BetaE12, p63 and thyroid transcription factor 1 (TTF-1) (Fig. 3A-B). The histologic pattern, in accordance with the radiologic findings, confirmed the diagnosis of abdominal metastasis of pulmonary origin. The recovery was uneventful, and the patient was discharged on the 15th post-operative day. During the follow-up the patient started chemotherapy, but he died 3 months after surgery.
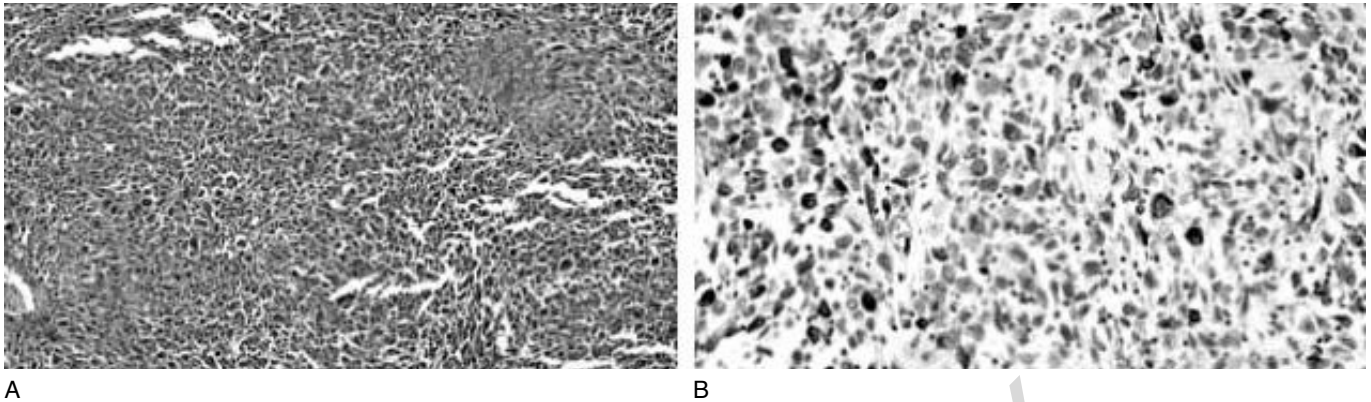
A   B

Fig. 3: A) Pathological analysis of metastasis by haematoxylin and eosin staining (original magnification, 10X): solid pattern of LCLC with cellular atypia, nuclear asymmetries and abundant eosinophilic cytoplasm; B) Immunohistochemical positive staining of antibody for Cytokeratin 7 (original magnification 20X).

CASE N. 2

A Caucasian, 62-year-old man was admitted to our Academic Emergency Department of General Surgery with hypovolemic shock due to severe gastrointestinal bleeding and abdominal pain. He had a 35-year history of smoking (40 cigarettes per day). During the previous 6 months, his medical history revealed a not-investigated asthenia, recurrent thoracic and abdominal pain and severe loss of weight. Laboratory tests showed marked anaemia and leucocytosis. Emergency CT-scan of the thorax and abdomen showed two lung nodules measuring 1.0 and 3.5 cm, respectively, as well as liver, adrenal, bones and mesenteric lymph nodes disease, intraperitoneal free air and fluids. An emergency laparotomy was performed, confirming the presence of intraperitoneal blood and a perforation due to two nodular lesions in the first jejunal loops (Fig. 4). A segmental jejunal resection followed by a mechanical side-to-end anastomosis was performed. Pathology examination revealed a metastatic lung adenocarcinoma with solid pattern involving small bowel (Fig. 5A).
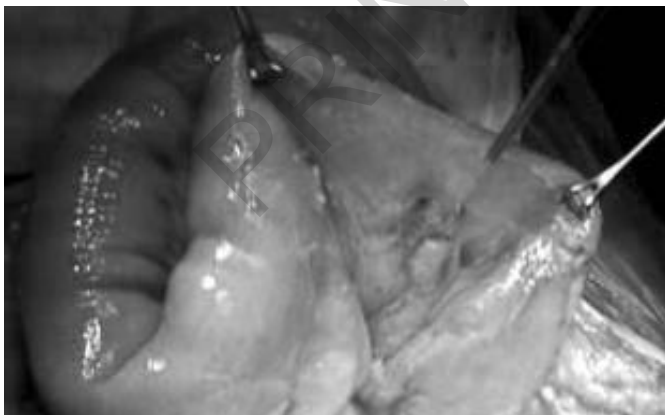

Fig. 4: Gastrointestinal metastasis from poorly differentiated adenocarcinoma. Surgical intraoperative evidence of a perforation in the first jejunal loops.

Immunohistochemical analysis was positive for CK-7 (Fig. 5B), carcino-embryogenic antigen (CEA) and TTF-1 (Fig. 5C). CK-20 (Fig. 5D) tested negative, confirming the diagnosis of metastasis of pulmonary origin. The postoperative recovery was uneventful, and the patient was discharged on the 15th post-operative day. During the follow-up he started chemotherapy, but he died 4 months after surgery.

Discussion

LC has various clinical presentations such as specific and non-specific respiratory symptoms, paraneoplastic syndromes, and/or symptoms occurring as the result of local or distant metastases [2]. The most common distant metastasis site of LC is the liver, while other intraabdominal metastases, such as GM, are uncommon, and associated with a poor prognosis [4,13].

As previously reported, only rare symptomatic cases have been published and, moreover, most of the data on GM from LC comes from autoptic studies that show an incidence of GM from LC higher than *in vivo* series of about 10% [9,14-17].

Indeed, Mc Neil et al [14] reported 46 small bowel metastases in 431 patients with primary lung cancer who underwent autopsy during an 11-year period with an average of 4.8 metastatic sites at the time of autopsy. On the other side, Ryo et al [18] in a 17-year study, have analysed 1,635 LC patients, and reported that metastases to the digestive tract (oesophagus excluded) were unexpectedly confirmed by surgery or autopsy in 30 of them. The major incidence of histological type associated with GM is still debated. In 1982, Antler et al [9], followed by Ryo et al [18] in 1996, reported that, according to their experience and the literature of those years, the most common histological type of LC related to GM was large cell undifferentiated carcinoma (3.7%), followed by adenocarcinoma (2.4%), small cell carcinoma (1.7%), and squamous cell carcinoma (0.7%). Conversely, in a recent
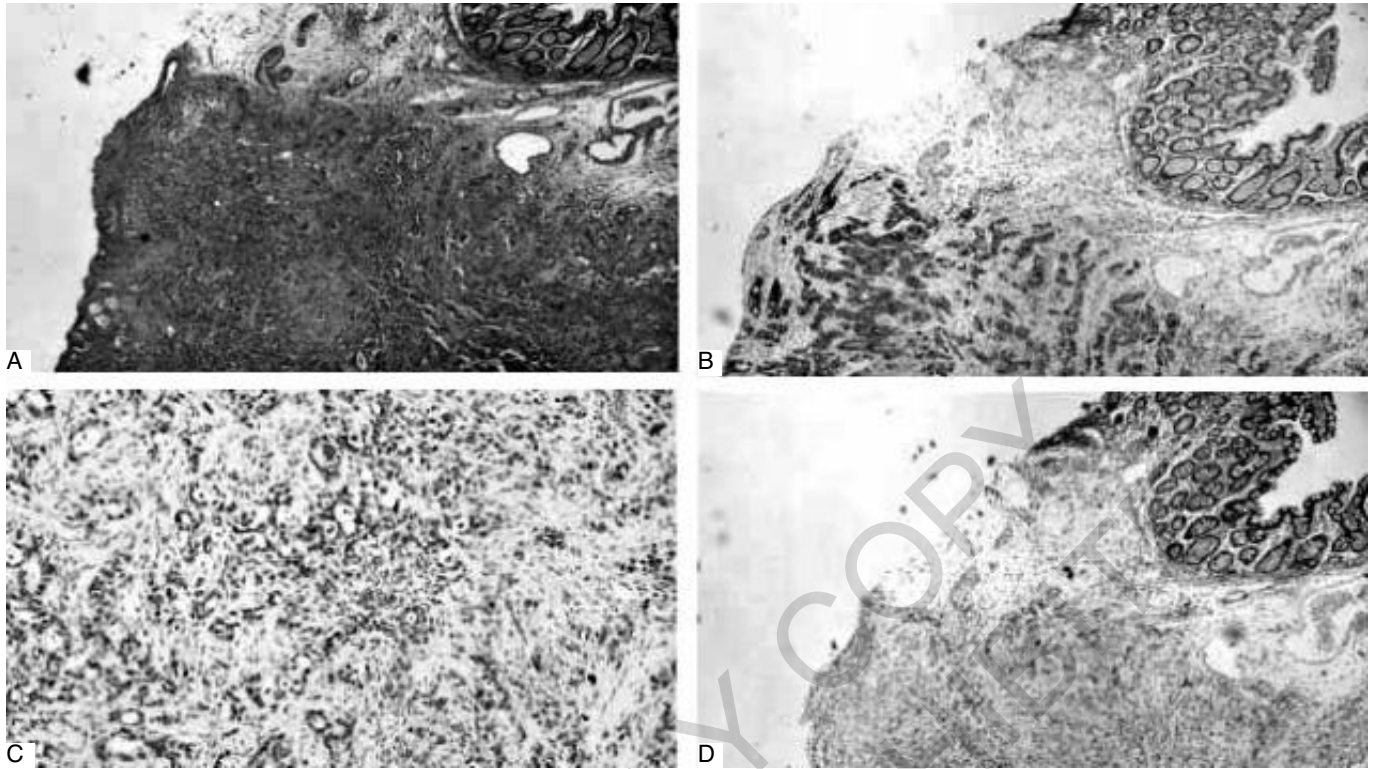
Fig. 5: A) Pathological analysis of metastasis by haematoxylin and eosin staining (original magnification, 10X); B) Immunohistochemical positive staining of Cytokeratin antibody 7 (original magnification 10 X); C) Immunohistochemical positive staining of TTF-1 (original magnification 20X); D) Immunohistochemical negative staining of Cytokeratin antibody 20 (original magnification 10 X).

systematic review of 366 cases, Hu et al [11] reported that the three most common histological types of LC identified in GM are squamous cell carcinoma, adenocarcinoma and large cell carcinoma with a reported incidence in the sample analysed of 28.5%, 27.6% and 20.9%, respectively. Nevertheless, when the histological distributions between GM from LC and primary LC histological type were compared, an increased frequency of metastases of large cell carcinoma, small cell lung cancer, and squamous cell carcinoma was reported compared with adenocarcinoma and other types of cancer [11].

The pathogenesis of intra-abdominal metastasis from LC involves both hematogenous and lymphatic spread and, owing to their abundant blood supply, small bowel represents the most common gastrointestinal metastatic site of LC: the jejunum is the most frequent site of involvement (50.9%), followed by ileum (33.3%) and duodenum (15.8%) [9,14,18,19]. Kim et al [20] in a study on 5,239 patients with LC, reported that GM were detected in 0.19% (10 cases) and small bowel metastases occurred in one-half of the patients, making it the most common metastatic site. Furthermore, Stenbygaard et al [13] reported that GM usually occur as a component of otherwise widespread metastatic diseases.

As suggested by the significant difference of incidence from clinical and autopsy studies, GM from LC were usually silent avoiding early diagnosis and sub-staging the disease, thus leading to delayed diagnosis. Symptoms related to GM always occur with the onset of gastrointestinal complications (obstruction, bleeding, perforation) and, presenting as acute abdomen, at first, they could be confused with other pathogenesis [20-23]. This statement is confirmed by our reported cases, both of them characterized by an acute clinical onset: in the first case with haemorrhage due to a gastric large ulcerated metastasis of LCLC and, in the second one, due to a very uncommon double area of perforation from a rare adenocarcinoma localization. Furthermore, Lee et al [21] showed that 21 of 8,159 (0.26%) patients had gastrointestinal metastases with 11 of them (52%) developing haemorrhage as leading cause of clinical presentation. Haemorrhage is more frequently detected in metastases that involved the gastric wall (52.8%), while occurs in the small bowel metastases and colorectum metastases in 15.6% and 32%, respectively. Hu et al [11] supposed that the probability and quantity of haemorrhage may depend on the incubation time of GM from LC and that the high capacity of growing for a longer period of time in the gastric cavity could justify the major incidence of gastric bleeding compared with other organs. For the same reason gastric metastases are rarely related to perforation and, above all, obstruction. Moreover, perforation is commonly related to small bowel metastases (63.7%) and, otherwise, it occurs in 11.5% of the colorectal

metastases[11]. The incidence of obstruction is equally reported for metastases involving small bowel (20.3%) and colorectum (20.7%), while it is quite higher in case of metastases of multiple organs (33.3%) [11]. Garwood et al [24] have suggested that different histological types of LC could exhibit different gastrointestinal complications although it may vary by region. Indeed, they have highlighted a predominance of small bowel perforations caused by adenocarcinoma in 23.7% - as in our second reported case - followed by squamous cell carcinoma (22.7%), large cell carcinoma (20.6%), and small cell carcinoma (19.6%). On the other hand, Hu et al[11] reported a lowest risk of perforation for adenocarcinoma compared with squamous cell carcinoma and SCLC. Some authors have showed an initial correlation with perforation and chemotherapy supposing that this one is the main cause of perforation in GM from LC [25,26]; nevertheless, it has not been confirmed in other studies which have supposed that ischemia, necrosis of metastases, obstruction and high pressure in the gastrointestinal cavity could determine bowel perforation [27].

Haemorrhage of GM from LCLC - as we report in our first case is usually more frequently described compared with haemorrhage of squamous cell carcinoma and SCLC. Moreover, sarcomatoid carcinoma shows the greatest likelihood of haemorrhage. The risk of haemorrhage may be decreased by chemotherapy, which may lead to tumour atrophy and ischemia [11]. Because of the acute clinical onset of GM from LC, CT scan is crucial for the diagnosis of patient with abdominal symptoms and LC [17]. Metastatic lesions were seen on CT scans as wall thickening, intraluminal polypoid or exophytic mass. Despite the high accuracy in the diagnosis of metastatic malignant sites, both PET-CT and capsule endoscopy have a controversial role due to their difficult employment in emergency setting and high costs [17]. However, PET/CT is able to assist the detection of subclinical metastases, but it should be used during the follow-up period to early diagnosis and evaluate extra-thoracic metastases [17,28-30]. Upper and lower endoscopy, when managed as bridge to surgery, as in the first reported case, are often useful in emergency to detect the cause of haemorrhage.

Pathology and, above all, immunohistochemistry are of paramount importance to correctly differentiate primary from metastatic LC. Immunohistochemical staining for TTF-1 is a reliable test for distinguishing primary adenocarcinoma and squamous cell carcinoma of the lung from metastatic adenocarcinoma. TTF-1, indeed, is highly specific for lung and thyroid adenocarcinomas but, occasionally, extrapulmonary tumours such as colorectal, gastric, cervical, endometrial, ovarian and breast ones, show positivity for TTF-1. Moreover, some pulmonary metastases from gastrointestinal, urologic and gynecologic tumors have been reported as TTF-1 positive [31-38]. In association with TTF-1, CK7 and CK20 should be examined to distinguish ovarian, pulmonary and breast carcinomas (CK7+/CK20-) from colon ones (CK7-/CK20+). Moreover, CDX2 is also a useful marker to differentiate adenocarcinomas of gastrointestinal origin from the pulmonary ones, since gastrointestinal carcinomas are CDX2+ [31-38]. As in LCLC diagnosed in the first reported case, poorly differentiated lung cancers can lose TTF-1 stain positivity and a multidisciplinary approach involving pathological history, clinical presentation and CT findings is fundamental to formulate a correct diagnosis. Even if there is no consensus about the best therapeutic management of GM in LC, surgery is mandatory as life-saving treatment when severe bleeding, bowel perforation or obstruction occur [39-41]. Moreover, surgery can relieve symptoms related to perforation, obstruction or gastrointestinal bleeding, but it cannot change the prognosis linked to LC which, in these cases of advanced disease, has inauspicious result.

The prognosis, indeed, is extremely poor as observed in these reported cases, since they showed a survival after the operation of 3 and 4 months, respectively [42]. The 1-year survival rate in patients with GM from LC was 20% and survival comes to nil at 2 years [40]. However, because of the primary disease, prognosis is still poor, and a mean survival time of 4 months is still reported [40].

Conclusions

In conclusion, the symptoms and signs of gastrointestinal metastases from lung cancer are difficult to recognize and often the diagnosis is delayed at the end stage of widely spread disease. Despite the rare clinical condition, in patients with a diagnosis of lung cancer managed in emergency surgery for gastrointestinal complication, the presence of gastrointestinal metastases from lung cancer should be suggestively taken into account, and potentially referred to the primary disease in order to tailor the best approach. In case of rare clinical manifestation complicated by unusual pathology or immunohistochemistry, a multidisciplinary approach with integration of surgical, radiological and pathological skills is mandatory for the correct diagnosis and in the correct management of the patient.

Acknowledgements

Riassunto

Il cancro del polmone rappresenta la seconda causa di morte negli Stati Uniti e l'alto tasso di mortalità potrebbe

essere correlato allo stadio della malattia al momento della diagnosi. Solitamente, infatti, la diagnosi si ottiene in uno stadio avanzato con documentabile coinvolgimento delle più frequenti sedi metastatiche quali: cervello, ossa, fegato, ghiandole surrenali, cavità toracica e linfonodi. Qualsiasi altra metastasi d'organo è molto rara e nel complesso si verifica solo nel 5% dei casi. Le metastasi gastrointestinali da carcinoma polmonare non a piccole cellule sono estremamente rare e in letteratura sono stati riportati solo pochi casi complicati da emorragia digestiva e/o perforazione. Riportiamo due casi di metastasi gastrointestinali e la loro rara associazione clinica con emorragia e perforazione intestinale.

Entrambi i pazienti sono stati ricoverati in regime d'urgenza. Nel primo caso si trattava di una paziente maschio di 59 anni giunto all'osservazione per un quadro di addominalgia ed emorragia gastrointestinale.

Un'esofagogastroduodenoscopia (EGDS) rivelava una lesione gastrica ulcerata associata ad evidenza TC di una massa polmonare destra il cui giudizio istologico risultava conclusivo per un cancro del polmone a grandi cellule.

Nel secondo caso un uomo di 62 anni presentava dolore addominale e shock ipovolemico da emorragia digestiva. Veniva sottoposto a una TC di emergenza che mostrava due noduli polmonari (1,0 e 3,5 cm di diametro) oltre a metastasi diffuse, pneumoperitoneo e versamento endoaddominale.

Entrambi i pazienti venivano sottoposti ad intervento chirurgico in regime d'urgenza. Nel primo caso veniva eseguita una asportazione *en bloc* della massa che coinvolgeva stomaco, colon destro e parte della parete addominale, mentre il secondo paziente veniva sottoposto a resezione segmentale del digiuno a causa dell'evidenza intraoperatoria di perforazione dovuta a lesione nodulare nella prima ansa digiunale. L'esame istologico definitivo ha rivelato l'origine metastatica di un tumore polmonare a grandi cellule nel primo caso e di una rara forma di adenocarcinoma polmonare nel secondo. Il periodo postoperatorio risultava regolare e, durante il follow-up, entrambi i pazienti hanno iniziato la chemioterapia. A seguito della prognosi tipica del carcinoma polmonare metastatico, i pazienti sono deceduti rispettivamente 3 e 4 mesi dopo l'intervento.

Nei pazienti con diagnosi di cancro al polmone che necessitano di un approccio diagnostico-terapeutico in regime d'urgenza per complicanze gastrointestinali, nonostante la rara condizione clinica, la presenza di metastasi gastrointestinali dovrebbe essere presa in considerazione e riferita alla malattia primitiva al fine di adottare la miglior strategia terapeutica.

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