

Anal Metastasis from Lung Cancer: Report of a Case and Systematic Review of the Literature

Ovidiu D. Bardac¹, Adina-Brîndușa Baciu^{2*}, Iancu S Bogdan-Duică³

¹First Surgical Clinic, Sibiu Emergency Clinical County Hospital, University "Lucian Blaga" from Sibiu, Romania

²Department of Bio-Medical Anthropology, Institute of Anthropology "Francisc I. Rainer" of the Romanian Academy, Bucharest, Romania

³Department of Pathology, Sibiu Emergency Clinical County Hospital, University "Lucian Blaga" from Sibiu, Romania

*Corresponding author:

Adina-Brîndușa Baciu, MD
Department of Bio-Medical Anthropology
Institute of Anthropology "Francisc I.
Rainer" of the Romanian Academy
Bucharest, Romania
E-mail: adinabaciu@yahoo.com

Abbreviations:

CT - computed tomography;
CK7 - Cytokeratin 7;
CK20 - Cytokeratin 20;
HMB45 - Melanosom;
HE, 20X - hematoxylin-eosin coloration,
20X lens;
SCLC - small cell lung cancer;
NSCLC: non-small cell lung cancer.

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Rezumat

Metastază anală a unui cancer pulmonar: prezentare de caz și revizuirea sistematică a literaturii

Introducere: Cu două milioane de cazuri noi înregistrate anual la nivel mondial, cancerul pulmonar este cea mai frecventă formă de cancer. În România cancerurile cu cea mai mare incidență sunt cancerul pulmonar la bărbați și cancerul mamar la femei. Mortalitatea prin cancer urmează același tipar. Peste 50% dintre pacienții cu cancer pulmonar prezintă metastaze la distanță în momentul diagnosticării bolii. Cancerul pulmonar metastatizează cel mai adesea în creier, oase, ficat și glandele suprarenale. Metastazele anale în cancerul pulmonar sunt extrem de rare. Conform studiului nostru au fost raportate doar 12 cazuri până în prezent.

Metode: Prezentare de caz și revizuire sistematică a literaturii. Am efectuat o căutare sistematică a literaturii de specialitate în baza de date PubMed utilizând următorii termeni: „metastaze în cancerul pulmonar” și „anal” sau „anus” sau „perianal”. Căutarea s-a efectuat de la începutul bazei de date și până în prezent. Limba de publicare a articolelor nu a reprezentat un criteriu de excludere.

Rezultate: Prezentăm cazul unei paciente cunoscută cu adenocarcinom pulmonar avansat care ni s-a adresat pentru o tumoră anală dureroasă, sângerândă și ulcerată. Tumora a fost excizată în anestezie rahidiană cu închiderea per primam a plăgii operatorii. Examenul anatomopatologic și imunohistochimic al piesei extirpate a pus în evidență o metastază de adenocarcinom

pulmonar. Au fost identificate și studiate 12 articole din literatura de specialitate, conținând 12 prezentări de caz. Raportul bărbați /femei a fost de 3/1. Vârsta medie a fost de 62,16 ani. Doar unul din cazuri avea o tumoră pulmonară cu celule mici. Celelalte 11 cazuri, de tip non-microcelular, au fost: 4 adenocarcinoame, 4 carcinoame cu celule scuamoase, 2 carcinoame nediferențiate și un carcinom mucoepidermoid. Metastazele anale au fost sincrone în patru cazuri și metacrone în restul de opt cazuri. Începând cu anul 2006 un rol important în diagnosticul acestor metastaze joacă imunohistochimia.

Concluzii: Pacienta noastră s-a prezentat cu o metastază anală de adenocarcinom pulmonar care mima o complicație a bolii hemoroidale. Datorită rarității lor, metastazele anale pot fi cu ușurință diagnosticate greșit. Din acest motiv, este recomandabil ca în diagnosticul diferențial al leziunilor ano-perianale ale pacienților cu cancer pulmonare avansate să fie luată în calcul și posibilitatea existenței unor metastaze. Echipele medicale implicate în tratarea acestor pacienți trebuie să cunoască această eventualitate patologică. Imunohistochimia joacă un rol deosebit de important în stabilirea diagnosticului tumorilor anale și perianale la pacienții cu neoplasm pulmonar.

Cuvinte cheie: cancer pulmonar non-microcelular, adenocarcinom pulmonar, metastază anală, chirurgie

Abstract

Background: Lung cancer is the most frequent cancer, accounting for over 2 million new cases per year worldwide. In Romania, the cancers with the highest incidence are lung cancer for men and breast cancer for women. Cancer-related deaths follow the same pattern. More than 50% of the patients with lung cancers have distant metastases at the time of diagnosis. Metastases from lung cancer occur mainly in the brain, bones, liver, and adrenals. Anal metastases from primary lung cancer are extremely uncommon. As far as we know there are only 12 cases reported in the literature until now.

Case report: Case report and systematic review. We performed a systematic literature search in PubMed using the following MeSH terms: "lung cancer metastasis" AND "anal" OR "anus" OR "perianal". The search was conducted from the beginning of the database onwards. No language exclusion criteria were used. We report the case of a patient with advanced lung adenocarcinoma presenting with a painful, ulcerated and bleeding anal tumor. The anal tumor was excised with primary wound closure in spinal anesthesia. The pathology report and the immunohistochemistry of the specimen revealed metastasis of the lung adenocarcinoma. The review included 12 papers reporting 12 cases. The male/female ratio was 3/1. The average age was 62,16 years. Among these 12 patients, one had a SCLC. From the remaining 11 cases with NSCLC, 4 were adenocarcinomas, 4 squamous cell carcinomas, two anaplastic carcinomas and one mucoepidermoid carcinoma. The anal metastases were synchronous in 4 cases and metachronous in the rest of 8 cases. Since 2006 immuno-histochemistry plays an important role in the diagnosis of these metastases.

Conclusion: Our patient presented an anal metastasis of a lung adenocarcinoma that was masquerading as a complicated hemorrhoidal disease. Because anal masses can be easily misdiagnosed, patients with lung cancers and anal or perianal complaints should be evaluated for metastatic disease. Medical teams that are managing such cases must be aware of this rare but possible situation. Immunohistochemistry plays an important role in establishing the diagnosis for the anal or perianal tumours in patients with lung cancer.

Key words: non-small cell lung cancer, lung adenocarcinoma, anal metastasis, surgery

Introduction

Today, cancer is one of the top health threats worldwide. The lifetime risk of developing cancer depends on many factors, including age, race, sex, genetics, and exposure to risk factors (1). According to GLOBOCAN 2018 data, lung cancer is the most frequent cancer for the global population, accounting for 11,6 % from all new cancer cases, corresponding to over 2 million cases per year worldwide. The leading cause of cancer-related deaths, for both sexes combined, is represented by lung cancer with 18,4 % from all cancer deaths, corresponding to about 1,8 million deaths per year worldwide. GLOBOCAN 2018 data reveal that in Romania the most common type of cancer is lung cancer for men and breast cancer for women while the most common type of cancer mortality follows the same pattern (2).

More than 50% of the patients with lung cancers have distal metastasis at the time of diagnosis (3). Through early systemic tumor spreading, metastases occur mainly in the lymph nodes, brain, bones, liver, and adrenals (3,4). Metastases seldom occur in uncommon places like skin, pancreas, spleen and gastrointestinal tract (4). Anal and perianal metastases from a lung carcinoma are extremely uncommon (4-6). There are only a few cases reported in the literature until now.

This article aims to present a patient with advanced lung adenocarcinoma that developed an anal metastasis mimicking a complicated hemorrhoidal disease.

Case Report

We present the case of a 69 years old woman, former heavy smoker. She was admitted to our surgical clinic in March 2018, for pains in the anal region accompanied by rectal bleeding. The symptoms occurred several weeks before and were interpreted by the patient as a consequence of the recent obstipation that occurred after a neurosurgical procedure she underwent in January that year. The patient also reported that she was diagnosed with lung cancer.

A lot of morbid conditions were mentioned in her medical record: a laparoscopic cholecystectomy performed several years before, a peripheral arterial occlusive disease stage IV Fontaine with a right common iliac artery angioplasty with stent insertion and associated right femoropopliteal artery bypass in 2015, arterial hypertension stage III and coronary artery disease.

We could find out the following medical history. On the 16th of December 2016, a thoraco-abdominal computed tomography revealed two pathological conditions: an iodophilic spiked tissue mass of 3,5/4 cm, located inferiorly and posteriorly in the left upper lobe of the lung, extending to the interlobar fissure and the hilum, associated with enlargement of the paratracheal and hilar lymph nodes up to 1,3 cm; a left adrenal tissue mass of 4,3/6 cm with retroperitoneal paraaortic lymph node enlargement up to 1,6 cm. The CT- scan result was highly suggestive for a primary lung tumor with left adrenal metastasis. The patient was further referred to the urology department where left laparoscopic adrenalectomy was performed on the 21st of December 2016. The histopathology revealed multiple metastases from a lung adenocarcinoma in the parenchyma of the left adrenal gland and the surrounding fat tissue. The postoperative course was uneventful. After the postoperative recovery, the patient went to another medical center to perform further investigations for the lung tumor. The diagnosis of lung adenocarcinoma stage IV: T2, N1, M1 was demonstrated and the indication for palliative chemotherapy was established. During the next months, the patient underwent 4 cycles of chemotherapy starting with Bevacizumab and continuing with the association of Carboplatin and Pemetrexed. In March 2017 chemotherapy was stopped because of poor results and bad tolerance. In September 2017 a new CT scan was performed that revealed a recurrence of the metastases in the left adrenal gland with the invasion of the left diaphragmatic crus and a small mass at the upper pole of the spleen. The lung tumor was relatively constant in shape and dimensions.

In January 2018 the patient was admitted

to the neurosurgical department for intracranial hypertension syndrome and mixed aphasia. A cerebral magnetic imaging resonance reveals a left frontal lobe intracerebral mass of 39 mm width interpreted as a subacute hematoma. On the 10th of January, the patient underwent surgical treatment to remove the tumor from the left frontal lobe. The postoperative course was uneventful with the improvement of the neurological status. Histology revealed a metastasis from the lung tumor.

A new CT scan, performed in March 2018 showed a global worsening of the disease with the enlargement of both the lung tumor and the left adrenal recurrence. Furthermore, the number of splenic metastases increased to three and an image suggestive for metastasis in the body of the 8th thoracic vertebra occurred.

At admission, the local clinical exam performed in lithotomy position revealed a moderately painful, 5/2 cm anal tumor at 7 o'clock, with both skin and mucosal ulceration (*Fig. 1*). The digital rectal exam showed a normotonic internal anal sphincter and no pathological findings above the dentate line. The development of the tumor seemed to be more towards the periphery and did not involve the internal anal sphincter.

The next day, on the 7th of March 2018 we underwent in spinal anesthesia the tumor excision with primary wound closure (*Fig. 2* and *3*). The postoperative course was uneventful. The patient was discharged on the second postoperative day.

A week after the discharge the patient presented herself again at the hospital for rectal bleeding. The clinical examination revealed a freshly occurred wound dehiscence. The stitches were removed and the wound was left open for secondary healing. After a week the patient was discharged in good clinical condition, without pain, bleeding or inflammation. The postoperative wound was partially healed and the patient presented no fecal incontinence.

The pathology report (no. 6565/6569) showed: nodular tissue infiltration with cells



Figure 1. Ulcerated anal tumour at 7 o'clock lithotomy position

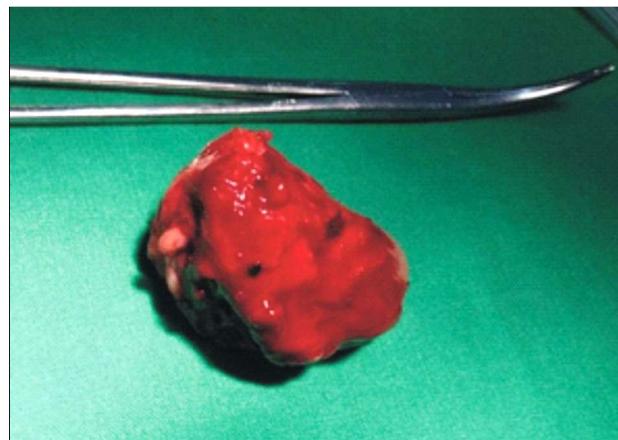


Figure 2. Operative specimen



Figure 3. Postoperative aspect

with moderate pleomorphism, more eosinophilic cytoplasm, vacuolization and isolated formation

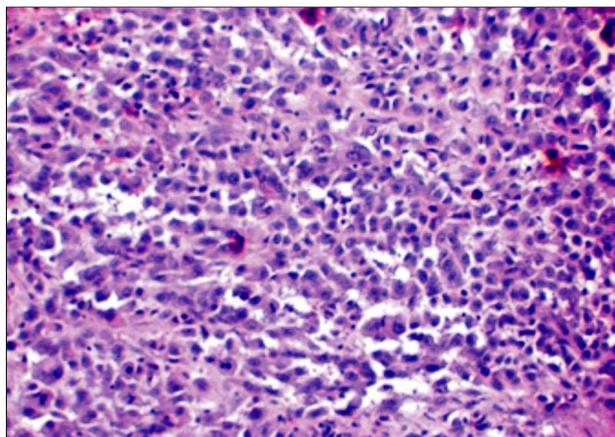


Figure 4. HE, 20X

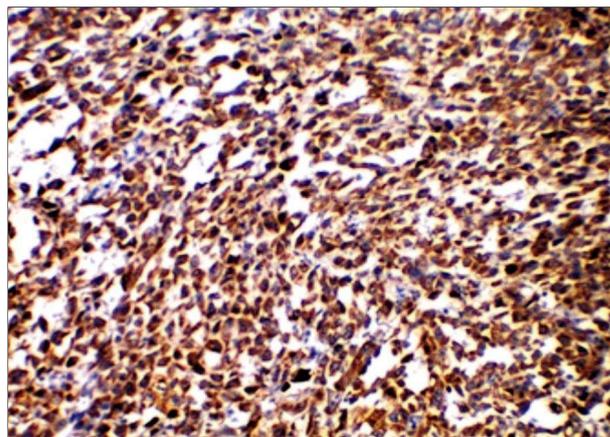


Figure 5. CK 7 positive, 20X

of positive alcian mucin; numerous mitosis; central necrosis and hemorrhage; moderate inflammatory reaction around (*Fig. 4*). The lesion is completely excised. The immunophenotyping revealed: Cytokeratin 7 (CK7) – positive (*Fig. 5*), Cytokeratin 20 (CK20) – negative, Melanosom (HMB45) – negative, Ki67-40%. Conclusions: metastasis of adenocarcinoma.

The case study was done by following the ethical norms of scientific research and the principles of anonymity and confidentiality.

Systematic Review of the Literature

We performed a systematic literature search in PubMed using the following MeSH terms: “lung cancer metastasis” AND “anal” OR “anus” OR “perianal”. The search was conducted from the beginning of the database till present. No language exclusion criteria were used. The search revealed 226 papers. From the 226 results only 12 papers were selected. The others were excluded being off topic. A second “reference in reference” search was performed and this revealed another two significant papers (9,17). All the 14 papers were case reports, except one that included also a literature review. This was the paper of Al-Tarakji at all. published in 2016 (18). During the process of final selection another two papers were excluded because the metastases were located in the gluteal regions (but-

tocks), separate from anus or perianal region. The first of these two cases was reported by Srikanth in 1999 (9) and the second by Tek in 2007 (10). The remaining 12 papers, reporting 12 cases, were accessed as follows: 10 in full text, 1 abstract (6) and title in 1 case (12). We kept this last paper because the work was cited as relevant by other authors. All important data, like gender, age, pathology, location and therapy of primary tumour, metastases localization and therapy, immunohistochemical confirmation were registered in a table (*Table 1*).

Results

Thorough literature research revealed only 12 reports of primary lung cancers that developed anal or perianal metastases (*Table 1*). The male/female ratio was 3/1, represented by 9 men and 3 women and the average age was 62.16 years. Among these 12 patients, only one had a SCLC, women, reported by Guerrera in 2014 (11). From the remaining 11 cases with NSCLC (4-6,12-19), 4 were adenocarcinomas (14, 15, 18, 19), 4 Squamous Cell Carcinomas (5, 12, 13, 17), 1 Mucoepidermoid Carcinoma (6) and two anaplastic carcinomas (4, 16). The surgical therapy of the primary tumour was attempted only in two cases: a right middle and lower lobectomy combined with left atrial wall resection (13) and a left pneumonectomy (19). In both cases the anal metastases devel-

Table 1. Primary lung cancers with anal metastases, reported cases

No.	Year	First Author	Gender	Age	Pathology	Primary tumour	Metastases	IHC*	Treatment and outcome of anal metastases
1	1968	Ger (5)	M	49	Well differentiated Squamous-Cell Carcinoma	Left superior lobe, no specific treatment	Anal canal, myocardium, syn**	no	Abdominoperineal resection, death in the 3 rd postop day
2	1975	Kanhouwa (4)	M	45	Anaplastic Large-Cell Carcinoma	Right upper lobe Radiotherapy and chemotherapy	Marginal anus, ulcerated, met *** (2 months) Inguinal lymph nodes, skin of the lower abdomen	no	Biopsy, radiotherapy and chemotherapy Survives 6 months
3	1988	Uemura (6)	M	78	Mucoepidermoid Carcinoma	No data available	Perianal skin and other, syn	no	Radiotherapy, dies in less than one year because of great hemorrhage from the perianal mass
4	1994	Kawahara (13)	M	75	Squamous Cell Carcinoma	Right lung; right middle and lower lobectomy combined with left atrial wall resection	Prolapsed anal canal polyp, 3 months, met	no	Transanal polypectomy, 9 months without recurrence
5	2006	Wisniewski (14)	M	53	Adenocarcinoma	Could not be identified	Anal abscess, 11 months, met Brain and mediastinal lymph nodes	yes	Incision, drainage; dies in 1 month
6	2010	Okutur (12)	M	64	Squamous Cell Carcinoma	No data available	Anal canal, polyp, met and pleural	No data	Excision and Radiotherapy
7	2012	Camus (15)	F	53	Moderately differentiated Adenocarcinoma, with clear cells	Left lung, palliative chemotherapy	non-healing perianal ulceration, Liver, subcutaneous, lymph nodes	yes	Biopsy, radio and chemotherapy
8	2014	Imai (16)	F	36	NSCLC, poorly differentiated carcinoma	left superior sulcus tumor, palliative radiotherapy	Haemorrhoid, painless perianal mass, met, Subcutaneous and multiple brain metastases	yes	Excision
9	2014	Guerra (11)	F	75	SCLC	Not specified, chemotherapy	Perianal abscess, 1 month later under Chemotherapy, met, and iliac bone metastasis	yes	Biopsy and chemotherapy
10	2014	Kiliç (17)	M	73	Squamous Cell Carcinoma	posterior segment of the upper lobe of the right lung	Perianal abscess and right adrenal, syn	no	Incision, biopsy, referred for adjuvant therapy
11	2016	Al-Tarakji (18)	M	75	NSCLC, Adenocarcinoma	Left-apical segment (Pancoast), palliative RT and Chemotherapy	Anal ulcerated mass, met (7 months) Liver, adrenal, chest wall	yes	Biopsy, dies in 1 month
12	2016	Dhandapani (19)	M	70	NSCLC, Adenocarcinoma	Left lower lobe, pneumonectomy, no chemotherapy	Perianal abscess 3 months later, met	yes	Incision, drainage, biopsy, dies in 2 weeks
13	2018	Our case	F	69	Adenocarcinoma	Left upper lobe, palliative chemotherapy	Anus (Haemorrhoidal thrombosis), met, 15 months Also adrenal, spleen, brain, spine	yes	Excision

*immunohistochemistry, ** synchronous, ***metachronous

oped in three months after surgery. In 8 cases was attempted only palliative radiotherapy and chemotherapy. For two cases the data are missing (6, 12). The anal metastases were synchronous in 4 cases and metachronous in the rest of 8 cases. For the last 8 cases the interval of occurrence varied between 1 and 11 months. Since 2006 almost all the cases were immunohistochemically confirmed. This started with the work of Wisniewski et al. (14). The

treatment of anal metastases consisted of biopsy and radiotherapy in 5 cases, incision and biopsy in 3 cases (for abscess like masses), excisions in three cases and an abdominoperineal resection.

Discussion

Lung cancer is categorized into two main histological groups: small cell lung carcinoma

(SCLC, 15% of all lung cancers) and non-small cell lung carcinoma (NSCLC, 85% of all lung cancers) (7,8). The main types of NSCLCs are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most common type of lung cancer, accounting for more than 40% of lung cancers and more than 50% of the NSCLC types (7). The incidence of adenocarcinoma has risen steadily over the past few decades.

Not only the pathologic type but also the stage of the disease and the general status of the patient are determinant factors for choosing the right therapy protocol (8). Curative therapy of lung cancer is strongly limited by the great number of patients diagnosed in advanced stages. More than 50% of lung cancer patients have distant metastases at the time of diagnosis (3). Anyway the perianal region is a very uncommon metastasis site. The literature research revealed 12 cases with anal or perianal metastases secondary to lung cancer. Our patient is a 69 years old woman, with a lung adenocarcinoma that subsequently developed an anal metastasis.

Including our case, the majority of anal metastases occurred in NSCLC (12 cases from 13). The reason for this fact could be the higher proportion of NSCLC among lung cancers (80-85%) and the higher aggressiveness of the SCLC that leads to much shorter survival periods.

The 12 reported cases of anal metastases from lung cancer embrace the following clinical patterns: 4 perianal abscess like lesions, 4 marginal anal masses (with or without ulcerations), 3 tumours of the anal canal (two polypoid), and 2 perianal nonhealing skin ulcerations. Remarkable is that all three metastasis located in the anal canal originate from a squamous cell carcinoma of the lung. These types of lesions are suitable for local excision when early diagnosed. All the other clinical forms of anal metastases suggest different stages in the evolution of the tumours, from nodular lesions, to necrosis, abscess formation and finally the development of ulcerations. In these cases, the early diagnosis in the nodular stage of the tumour is very

important for the surgical treatment. The histological pattern of these tumours is variable, all types of NSCLC being encountered.

In our case, the anal metastasis being early diagnosed, could be operated with good results. Complete local excision of the nodular lesion with mucosal ulceration located at the anal verge was performed (*Figs. 2 and 3*). The pathology report demonstrated the removal of the entire tumor. In our opinion, this should be the attitude whenever is possible. Good results with local excision were reported also by other authors (12,13,16) even though, two of them were performed for polypoid metastatic tumours. In opposite, invasive surgery like abdominoperineal resection could lead to disastrous results as previously reported (5). Most of the cases reported in the literature were treated by surgical drainage of abscess-like masses associated with biopsy, or biopsy alone with adjuvant radiotherapy (6,11,14,15, 17,18,19). The results are not so good as in the radical excision because the metastases evolve developing a lot of complications that significantly alter the quality of life for these patients (4). A case of death due to massive bleeding from a reccured perineal metastasis is also reported in the literature (6). Even though the surgical excision will not improve the survival rate, will improve the quality of life for these patients. In large infected, exulcerated anal metastasis, when the surgical resection is not feasible a palliative colostomy should be taken into account.

Most of the reported cases presented also other secondary deposits at the time of the anal metastasis diagnosis. Our patient had adrenal, splenic, cerebral and spinal metastases. Moreover, our patient underwent three surgical procedures, from December 2016 to March 2018, and none of those addressed to the primary tumor but only to the metastases. The diagnosis of lung adenocarcinoma was preceded by the left laparoscopic adrenalectomy.

The anal metastasis was histologically and immunohistochemically documented. The tumor cells were positive for CK7 (*Fig. 5*) and negative for CK20 revealing an adenocarcinoma of lung origin while adenocarcinomas of colo-

rectal origin are mostly CK7 negative / CK20 positive (14).

Conclusions

Anal or perianal metastases in primary lung cancers are very rare. According to our knowledge, our case is the 13th reported in the literature. Our case proves that if the diagnosis of the anal metastasis is early a complete surgical excision is possible and appropriate. The surgical excision is easily feasible in polypoid like metastasis originating from the anal canal or in the nodular stage of the perianal metastasis, before the development of necrosis, abscess and ulceration. The complete surgical excision should be performed whenever it is possible because other treatments, like radiotherapy, can only temporarily alleviate the local situation. The tumor will regrow, will develop cutaneous and mucosal ulcerations, infection, bleeding and eventually anal stenosis. In such cases performing a colostomy could be the right and only option. The surgical excision is only possible when the metastasis is early diagnosed. This is the reason why the medical teams that are managing such cases must be aware of this rare but possible situation.

Including our case, the majority of anal metastases occurred in NSCLC (12 cases from 13). The reason for this fact could be the higher proportion of NSCLC among lung cancers (80-85%) and the higher aggressiveness of the SCLC that leads to much shorter survival periods. We noticed a correlation between the histological type of squamous cell carcinoma of the lung cancer and the polypoid metastases, located in the anal canal. This aspect should be further investigated.

As previously mentioned, more than 50% of lung cancer patients have distant metastases at the time of diagnosis (3). This fact drastically limits the indication of curative therapy. Even though curative treatment is not indicated, the patients with metastatic lung cancer need frequent surgical palliation. Among these situations is the rare case

of developing an anal metastasis. A proper diagnosis and management of this situation brings a lot of improvement in the quality of life of these patients.

Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

Ethics Approval

The case study was done by following the ethical norms of scientific research and the principles anonymity and confidentiality.

Authors' Contributions

Ovidiu D Bardac: conceptualization, methodology, investigation, writing - original draft. Adina-Brîndușa Baciuc: writing - review & editing, visualization. Iancu S Bogdan-Duică: methodology, investigation. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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