A Double Primary – Diffuse Large B-Cell Gastric Lymphoma with Concomitant Non-small Cell Lung Adenocarcinoma "The Great Pretender"

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ABSTRACT

Multiple primary tumors are rare with the prevalence of 0.734% to 11.7%. Detecting these tumors presents as a diagnostic dilemma which affects treatment and prognosis of these patients.

This is a case of a 79-year-old, male with metachronous malignant lesions in the lung and stomach. He initially presented with non-productive cough, hematemesis, and a pulmonary mass upon chest X-ray. CT guided biopsy was done and showed pulmonary tuberculosis but the patient refused treatment. He later presented with melena in which an endoscopy revealed gastric ulcer and biopsy of gastric adenocarcinoma. Patient underwent laparoscopic subtotal gastrectomy with Roux-en-y Gastrojejunostomy. However, final histopathology of the stomach revealed gastric lymphoma.

Chest CT scan showed increased size of the lung mass and biopsy done revealed lung adenocarcinoma. Patient is now diagnosed with metachronous double primary of non-small cell lung adenocarcinoma stage IIIA (pT4N0M0) and gastric lymphoma stage IIIA (pT4aN2M0). Patient underwent osimertinib chemotherapy for the non small cell lung adenocarcinoma and a pre-treatment phase of vincristine, then six cycles of CHOP-R (cyclophosphamide, doxurubicin, vincristine and prednisone with rituximab regimen) for the gastric lymphoma.

Key words: Large β-cell gastric lymphoma, pulmonary tuberculosis

The term multiple primary malignant tumor was first defined as when each of the tumor must be of different histological type and possibility of metastasis excluded.[1] To the author's knowledge, only a few cases of simultaneous occurrence of lung adenocarcinoma with concomitant gastric lymphoma has been reported as stated where a patient presented with synchronous lung adenocarcinoma and extranodal marginal B-cell lymphoma of mucosa associated lymphoid tissue.[2] Another case presented also stated a lung adenocarcinoma and synchronus B-cell lymphoma of the stomach in a 60- year old man.[3] Lung and gastric cancers are the first and second leading causes of death from cancer worldwide, and are especially prevalent in Eastern Asia. Relatively few reports[4,5] are available in relation to the treatment and outcome of synchronous and metachronous lung and gastric cancers, although there are increasing numbers of patients with these disease.

Lymphoma is a cancer of the lymphatic system which is part of the body's fighting network against infection. It can be classified into Non-Hodgkin lymphoma- (NHL) and Hodgkin lymphoma- (HL). Non-hodgkin lymphoma is hematologic malignancy that came from B cells, T cells, or rarely natural killer cells while Hodgkin lymphoma is type of hematologic malignancy in which characteristic, large, dysplastic mononuclear and multinucleated cells are bounded by mixtures of mature, non-neoplastic, inflammatory cells and fibrosis. Lymphoma can affect lymphatic glands and other areas throughout the body including

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the stomach, which is the most frequent extra nodal site. Primary gastric lymphoma accounts for <2% of gastric malignancies and 2% of all lymphomas which is relatively.[6] Like gastric adenocarcinoma, H. pylori infection increases the risk for gastric lymphoma. The gastrointestinal tract is the most common extranodal site for lymphoma, accounting for 15-20% of all cases of extra nodal lymphoma.[7] The most common sites of involvement include the stomach followed by the small intestine and ileocecal region. In this report, the author presents and briefly reviews the clinicopathological features of a patient who developed cough and gastrointestinal bleeding caused by a non-small lung cancer and diffuse large B-cell gastric lymphoma which are of different histology.

Neoplasms of the lung can be classified into small cell lung cancers and non-small cell lung cancers. Lung adenocarcinoma arises from the bronchial mucosal glands, and it falls under non-small cancer which is the most frequent histotype. It is the most commonly observed subtype in non-smokers and usually occurs in a peripheral location within the lung, in some cases at the site of pre- existing scars, wounds, or inflammation.

Management of lung cancer pre-treatment evaluation includes pulmonary function test, bronchoscopy,pathologic mediastinal lymph node evaluation, brain magnetic resonance imaging-(MRI) with contrast, MRI with contrast of spine plus thoracic inlet for superior sulcus lesions abutting the spine , sublcavian vessels or brachial plexus, positron emission tomography (PET). Depending on the stage of patient chemotherapy, radiotherapy and surgery are recommended, more importantly immunohistechemical staining with epidermal growth factor (EFGR) and thyroid transcription factor 1 (TTF-1), napsin A for lung adenocarcinoma and p40 , p63 for squamous carcinoma marker. Surveillance after completion of definitive therapy wiith chest CT scan with contrast evrey six months for two to threee years for stage I-II and every three to 6 months for three years in stage III or IV along with smoking cessation advice, counseling and pharmacotherapy.

Gastric cancer workup include comprehensive physical examination, laboratory evaluations, testing of H, pylori infection status, appropriate imaging studies which include CT scan with contrast of diagnostic quality for chest, abdomen, and pelvis, endocopic ultrasound . If Helicobacter pylori infection is proven, eradication with proton pump inhibitor along with combination of antibiotics including clarithromycin and amoxicillin should be done. Depending on the stage of the patient immunotherapy, chemotherapy, radiation therapy and surgery is recommended.

It has been said that the criteria to characterize cases of multiple primary tumors can be defined as two or more independent primary reportable neoplasms, arising as lesions in the same or separate organs or anatomical portions of the body of an individual. If the cancer is distinct in cellular composition and came from a different site than the original tumor it is a separate primary, as well as cancers of different histologic types in the same site.

The objectives of this report include the following:

1. To present a case of diffuse large B-cell gastric lymphoma with concomitant non-small cell lung adenocarcinoma.
2. To discuss the management of a patient with metachronous tumors

THE CASE

This is a case of a 79-year-old male who initially presented with non- productive cough nine months prior to admission with an assessment of pneumonia. There was no associated fever, difficulty of breathing nor shortness of breath. No heredofamilial history of cancer. Initial chest radiographic examination showed an ovoid opacity in the right cardiophrenic angle measuring 8.12cm x 6.32 cm. Further imaging evaluation with non-contrast enhanced CT scan of the chest showed a large lobulated soft tissue mass at the posterior right lower lobe, 7.4cm x 8.1cm x 8.8cm. No evidence of right bronchovascular encasement or invasion. Hence, CT-guided percutaneous needle aspiration biopsy of the lung mass was negative for malignant cells with cytomorphologic features consistent with a chronic granulomatous inflammatory process to consider tuberculosis. He was advised to complete six months of anti-koch's treatment, however the patient refused.

Three months prior to admission, the patient had episodes of epigastric pain with associated hematemesis and melena. Patient had a history of blood transfusion due to hemoglobin count of 7.2g/dL secondarily due to the aforementioned symptoms. Work-up was done to determine the source and cause of bleeding with imagings like wole abdominal ultrasound which was requested for further examination and appeared to have a small liver cyst at right lobe; enlarged prostate gland of 65.3

grams grade III with few parenchymal concretions .Three weeks prior to admission due to persistence of hematamesis and melena, further investigation with an esophagogastroduodenoscopy revealed a huge gastric ulcer Forrest Classification Type 3, erosive gastritis, Helicobacter pylori infection with consideration of malignancy as shown in Figure 1A, 1B and 1C.

The H. pylori infection was medically eradicated with sequential therapy of: Esomeprazole 40mg/cap twice a day, Clarithromycin 500mg/tab twice a day, Levofloxacin 500mg/tab once a day. Biopsy was gastric adenocarcinoma.

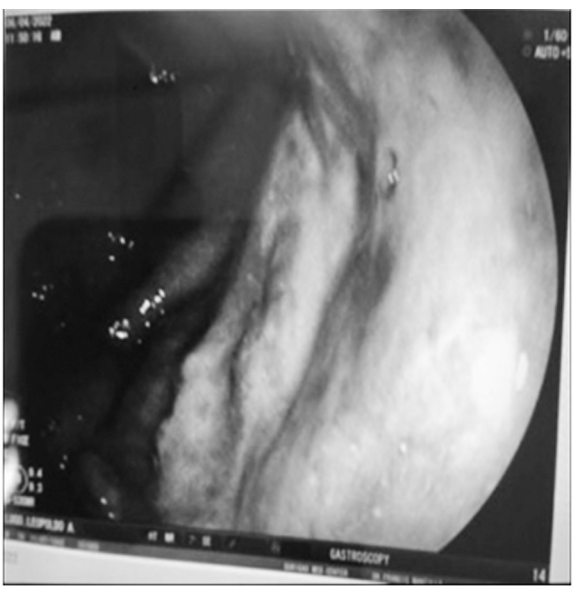

Figure 1A. Esophagogastroduodenoscopy images done last April 26,2022 presenting the huge gastric ulcer Forrest Class III.

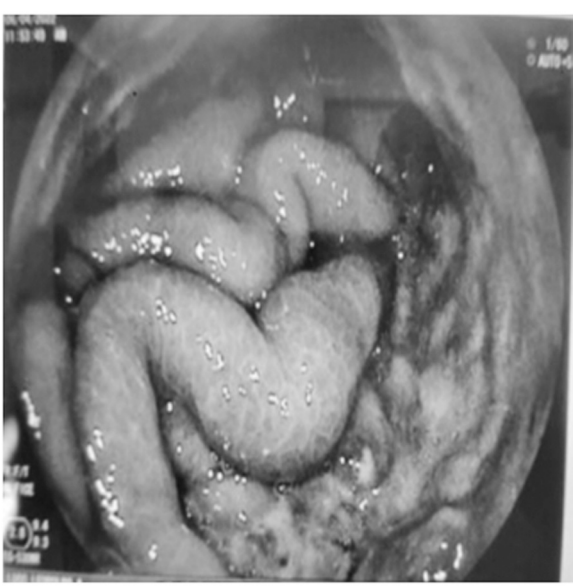

Figure 1B Esophagogastroduodenoscopy images done last April 26.

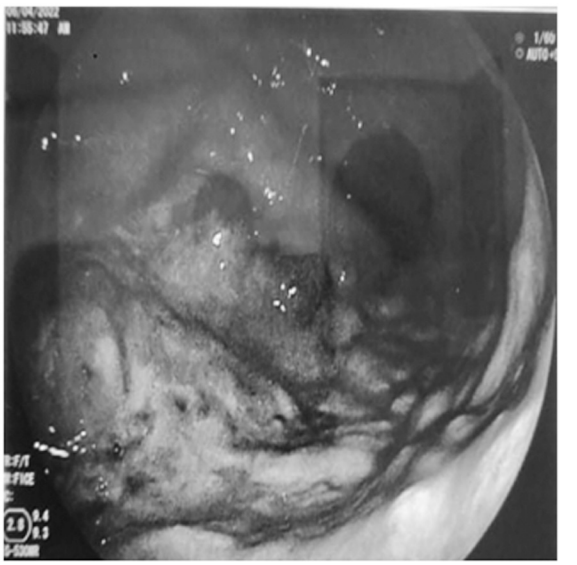

Figure 1C. Esophagogastroduodenoscopy images done last April 26,2022 presenting the erosive gastritis

Moreover, the following day a non-contrast enhanced computed tomography scan of the whole abdomen was done to determine the mass which was seen at the esophagogastroduedeonscopy which showed a suspicious asymmetrical wall thickening at the gastric body measuring 2.5cm in thickness with adjacent lymphadenopathies at the perigastric and lesser curvature with largest size at 1.6cm, ruling in neoplastic process. There is also a note of osteolytic destruction at the right pelvic wing; wherein bone metastasis was suspected.

One week prior to admission the patient decided to seek for second opinion and consulted at our institution still with persistence of symptoms of hematemesis, melena, epigastric pain and now with early satiety. He also had significant weight loss from 86 to 74kg and was admitted with a working diagnosis of upper gastrointestinal bleeding secondary to gastic mass and acute anemia. He was managed initially for nutritional build up. Blood work up was normal with decreased potassium at 2.95 mEq/L which was eventually corrected. Repeat whole abdominal CT scan with contrast to assess the extent of the gastric mass ,lymph node extension, and or to evaluate for infiltration of the adjacent structures, as depicted in Figure 2A, 2B- demonstrated progression of the asymmetrical gastric wall thickening to 2.7cm (previously 2.5cm), no evident luminal narrowing.

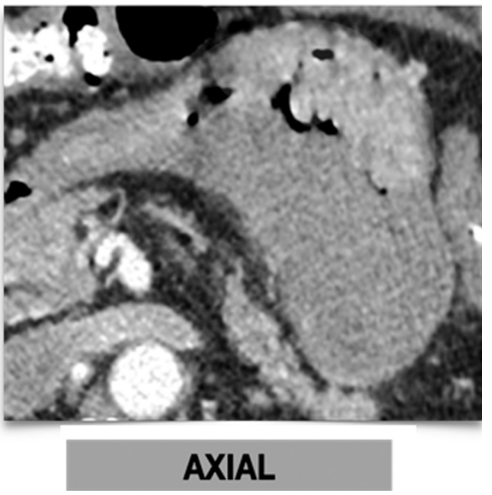

Figure 2A. Whole abdominal CT scan with contrast with the gastric wall thickening highlighted in yellow in axial view.

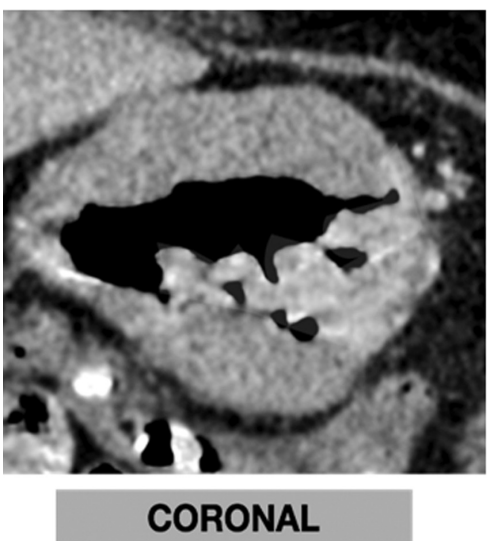

Figure 2B. Whole abdominal CT scan with contrast with the gastric wall thickening highlighted in yellow in coronal view.

As for the lung mass, repeat chest CT scan with contrast, as shown in Figure 3A & 3B was done also to better delineate its extent and to confirm if there was growth or development of the solid component which showed enlargement to 10.3cm x 8.9cm x 7.3cm (previously 7.4cm x 8.1cm x 8.8cm) described as multi-septated complex mass with consideration of metastatic vs. neoplastic process. Multiple non-enhancing, non-calcified pulmonary nodules, unenlarged to prominent sized mediastinal lymph nodes with largest at 0.9cm considering metastatis versus primary neoplastic process.

After the patient's nutritional build up , weight gain and electrolyte imbalance corrected, he underwent surgery to stage the patient's condition so as to determine the appropriate treatment for

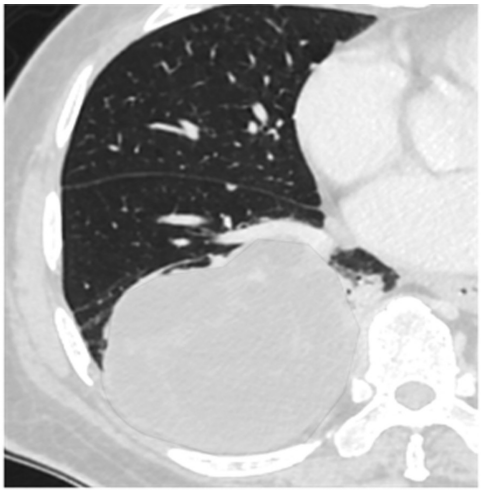

Figure 3A. Chest CT scan with contrast axial view of the heterogenously enhancing multi- septated complex mass highlighted in yellow seen in the posterobasal segment of the right lower lobe measuring 10.3cm x 8.9cm x 7.3cm. Heart seen anteriorly.

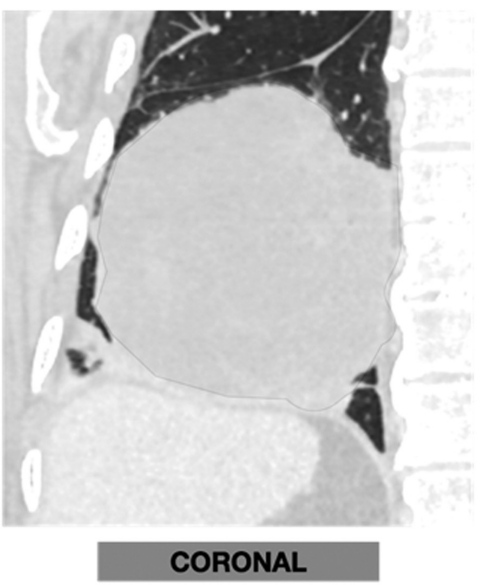

Figure 3B. Chest CT scan with contrast coronal view of the heterogenously enhancing multi-septated complex mass seen in the posterobasal segment of the right lower lobe measuring 10.3cm x 8.9cm x 7.3cm. Spine located medially.

him and remove the gastric mass which is the most propable cuase of his blood loss. Intraoperative findings as seen in Figure 4A revealed a gastric mass 12 cm in diameter located at the lesser curvature extending to the greater curvature of the stomach, no carcinomatosis or other lesion seen, laparoscopic subtotal gastrectomy (Hoffmeister); Roux-en- Y gastrojejunostomy was performed. Porta-

cath insertion was also done for further plans of intravenous chemotherapeutic intervention that would cover both lesion post-operatively. On the other hand one week postoperatively, ultrasound guided core needle biopsy was done to the lung mass for further workup that would give the proper identification of the type of lung mass it is to give the appropriate treatment for the patient.

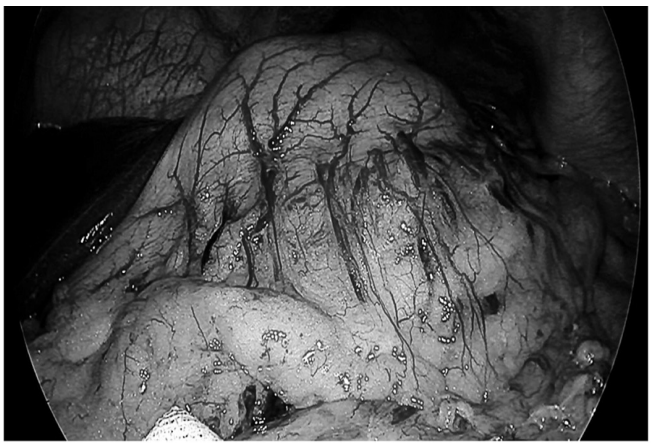

Figure 4A. Intra-operative findings showing the mass at the gastric body not yet resected with intact blood supply.

Post-operatively the total parenteral nutrition was continued and on the third post-operative day general liquid diet was started and progressed to soft diet on the fifth post-operative day which he was able to tolerate. Early recovery after surgery was done, he may sit on bed and dangle feet at bedside. Patient has improved health status ,hence, discharged on the seventh post-operative day. Then on the tenth day the sutures were removed as well as the Jackson- Pratt drain without any signs of infection. It was placed to evaluate if there would be leak from the anastomosis done during the operation.

Histopathologic examination of the gastric mass as illustrated in Figures 5A and 5B showed a malignant round cell tumor favoring lymphoma with a full thickness infiltration of the gastric wall and direct extension to the perigastric fat. Tumor size of 9 cm in greatest dimension with lymphovascular invasion and five out of thirty three regional lymph nodes were positive. Proximal and distal margins were negative for tumor . Histopathology of the ultrasound guided biopsy report of the lung mass favoring adenocarcinoma, non-small cell with the microscopic findings as shown in Figures 6A ,6B and 6C.

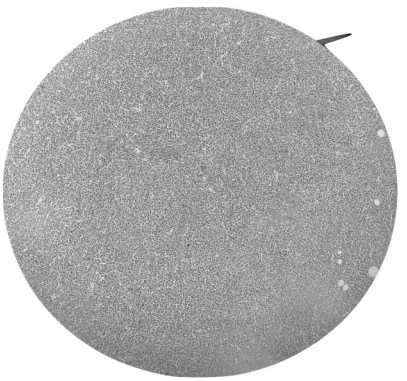

Figure 5A. Microspcopic imaging of the gastric mass

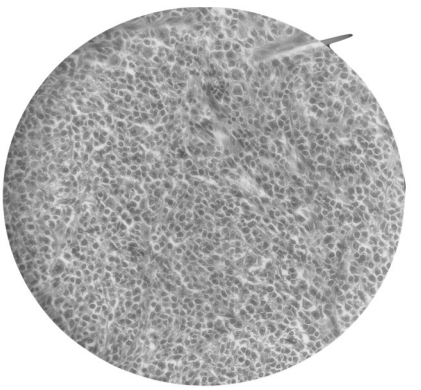

Figure 5B. Microspcopic imaging of the gastric mass.

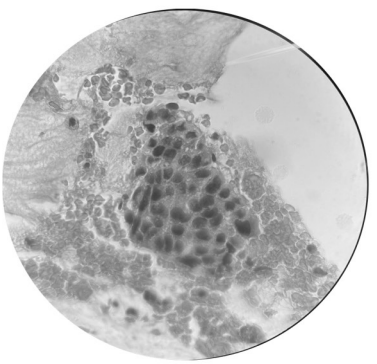

Figure 6A. Microspcopic imaging of the lung mass

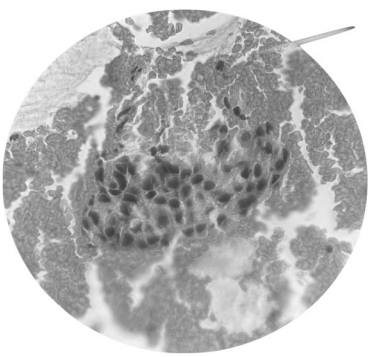

Figure 6B. Microspcopic imaging of the lung mass.

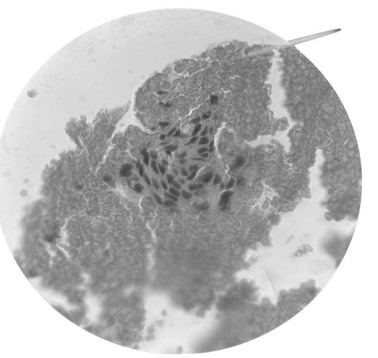

Figure 6C. Microspcopic imaging of the lung mass

To examine whether gastric tumor was a primary cancer or a metastasis, as well as to examine its histological origin, immunohistochemistry testing was done for the gastric tumor which revealed CK negative, LCA diffusely positive, CD3 negative staining on cells of interest, positive on few scattered T cells, and CD20 diffusely positive on tumor cells of interest meaning patient has a primary diffuse large B-cell gastric lymphoma.

The current management for the lung adenocarcinoma is osimertinib chemotherapy while waiting for the immunohistochemical staining and for the gastric lymphoma is pre-treatment phase with vincristine with prednisone, then six cycles of (CHOP-R) cyclophosphamide, doxurubicin, vincristine and prednisone, rituximab regimen.

DISCUSSION

The author was presented with a case of two separate lesions with different histopathologic results on two different occasions. The result of diagnostic studies revealed a rare- co-existence of lung adenocarcinoma and gastric lymphoma as supported by case made by Sun, et al. 2015[3] where they reported a rare case of synchronous primary pulmonary adenocarcinoma and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. Different histology may be identified simultaneously or at different times as synchronous or metachronous tumors.[7] The timeframe to call a tumor based on the two groups varies. Some would claim that synchronous tumors occur when the second primary was diagnosed two months from when the first primary tumor or less than or equal to six months while the second group, the metachronous is if more than two months have passed when the second primary is diagnosed or it occurred more than six months apart.[1]

In the case presented to examine the origin and histopathology of the gastric mass and lung mass, immunohistochemistry testing of the gastric tumor showed CK negative meaning that the it is not a carcinoma, LCA diffusely positive meaning that it is a lymphoma, CD3 negative staining on cells of interest, positive on few scattered T cells meaning it is not of T cell-origin but rather a B-cell based on the CD20 diffusely positive on tumor cells of interest . Given the interpretation and reading of the immuhistochemistry , the patient has a primary diffuse large B- cell gastric lymphoma. For the lung mass he was EGFR positive which could favor squamous cell carcinoma of lung and 80% of non-small cell lung cancers.

Immunohistochemical staining is important in differentiating primary lung tumors from metastatic tumors. Immunohistochemistry used are keratins to subclassify primary lung tumors, and CK7 and CK20 as the markers oftenly used. It has been illustrated that primary lung carcinomas usually express CK7+/ CK20-, while on the other hand gastrointestinal carcinomas have the CK7-/CK20+ pattern.[8]

The immunohistochemistry staining of the lung mass revealed EGFR positive, TTF-1 negative, CK7 and CK20 negative with which we could derive that the lung mass could be a squamous cell or a small cell lung carcinoma. To further classify and confirm the type of lung mass, the p63 gene is recommended to have been tested and if turns out to be negative it is a small cell lung carcinoma and a squamous cell lung carcinoma if positive.

CONCLUSION

The occurrence of multiple primaries such as this case of diffuse large B- cell gastric lymphoma and lung carcinoma is not only rare but may also result in simultaneous treatment of each cancer making the management and treatment a challenge. Few cases have been stated like the double primary our patient presented, making it hard for physicians to start the appropriate treatment for him not knowing at first which is the primary problem or are they of the same type. In the present case tissue diagnosis was needed with the immunohistochemistry to choose the appopriate management and treatment for each pathology. It is of utmost importance to identify if a mass is a primary tumor or a metastasis so as to help physicians in choosing the appropriate treatment and intervention for patients.

In this case, and of other similar scenarios differentiating between primary lung cancer metastasizing to gastrointestinal tract and metastatic GI tumors in cryptic cases, it is valuable to use immunohistochemistry. Primary gastric lymphoma is a far more treatable case than adenocarcinoma of the stomach, a fact that underscores this need for making the correct diagnosis. Antibiotic treatment to eradicate H. pylori infection has led to regression of about 75% of gastric mucosa associated lymphoid tissue- (MALT) lymphomas and should be considered before surgery, radiation therapy, or chemotherapy is undertaken in patients having such tumors. Furthermore, surgery should be done for gastric mass and is said to be essential in preventing

life- threatening complications such as bleeding , obstruction and perforation. Subtotal gastrectomy, usually followed by combination chemotherapy, has led to 5-year survival of 20-40% in patients with localized high grade lymphomas. It would also be of significance in providing effective palliation as well as long-term survival for patients.

While they are rarely reported, the incidence of concurrent tumors may be expected to increase as a result of advancements, discoveries and improved sensitivity in diagnosing diseases along with widespread use of screening and staging methods and will most probably be seen often in the future as a result of improvements in diagnosis and treatment of cancers.

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