AMERICAN JOURNAL OF MEDICAL AND CLINICAL SCIENCES, 2023
VOL 8, NO. 4, PAGE 1 – 5

RESEARCH ARTICLE

Open Access

An Unusual Case of Triple Synchronous Malignancies in a Middle-Aged Male Smoker: A Case Report and a Brief Literature Review.

Mark Bannon[1], Creticus Marak[2]*, Stephen T Bastible[1], Adrita Ashraf[1], Achuta Kumar Guddati[3] and Prashant Kaushik[4]

[1]Department of Internal Medicine, House Staff, Northeastern Health System, Tahlequah, OK, USA.
[2]Department of Medicine, Pulmonary and Critical Care Medicine, Northeastern Health System, Tahlequah, OK, USA.
[3]Division of Hematology/Oncology, Augusta University, Augusta, Georgia, USA.
[4]Division of Rheumatology, Northeastern Health System, Tahlequah, OK, USA.

ABSTRACT

The presence of multiple primary malignant tumors (MPMTs) in a single individual is unusual. Depending on when the tumors are diagnosed, they can be classified as synchronous or metachronous. In the literature, metachronous tumors are more frequently described than synchronous ones. The vast majority of synchronous tumor cases involve two primary tumors, usually located in the same anatomic location, such as the prostate and bladder; or esophagus and stomach – organs that have been subject to field cancerization. A triple synchronous tumor arising in different anatomical locations is extremely rare. We present a unique case of a middle-aged man with synchronous lung, esophageal, and renal cancers.

ARTICLE HISTORY

Received 07 Sep 2023
Accepted 20 Oct 2023
Published 27 Oct 2023

KEYWORDS

Synchronous, Metachronous, Multiple Tumors, Triple, Malignancy, Lung Adenocarcinoma, Esophageal Carcinoma, Renal Cell Carcinoma.

Keywords

Synchronous, Metachronous, Multiple Tumors, Triple, Malignancy, Lung Adenocarcinoma, Esophageal Carcinoma, Renal Cell Carcinoma,

Introduction

Multiple primary malignant tumors (MPMTs) present unique diagnostic and treatment challenges to clinicians. Multiple primary malignant tumors (MPMTs) were first described by Billroth in 1889 [1]. A half-century later, Warren and Gates proposed the criteria for identifying multiple primary malignant tumors. The authors recommended meeting the following criteria for diagnosing MPMTs: tumors should have a definite malignant picture; tumors should be histologically distinct; and metastasis should be excluded [2]. Differentiating between synchronous and metachronous tumors can be confusing due to the different definitions used. A tumor is considered an index if no prior record of a malignant tumor exists. In the Surveillance Epidemiology End Results database, multiple tumors are considered synchronous if they are histologically distinct, arise at different anatomical sites, and are diagnosed within two months of each other [3]. The International Association of Cancer Registries and the International Agency for Research on Cancer recommend a 6-month cut-off time [3]. Both groups suggested using different anatomic sites to prevent the misclassification of multifocal and metacentric tumors in the same organ as multiple primary tumors.

Over the past few years, there has been a steady increase in synchronous malignancies reported in the literature, with approximately 1.7% of newly diagnosed malignancies having at least a second primary malignancy [4]. Based on the available data, the incidence of triple synchronous tumors/malignancies is estimated to be close to 0.5%, and that of the quadruple is only 0.3% [5]. Clinical underreporting, inadequate diagnostic workup, especially in resource-limited third-world countries, and different definitions may explain the paucity of literature on MPMTs. Our literature review found only 76 documented cases of triple synchronous MPMTs, most of which were reported recently. A patient with triple synchronous MPMTs of the lung, esophagus, and kidney has never been described before to the best of our knowledge.

Case Description

In August 2021, a 61-year-old male smoker with a history of 45 pack-years presented to his primary healthcare provider with "suprasternal notch" pain. His past medical history was not significant. There was no history of cancer in his family. He previously worked for an insulation company that may have exposed him to asbestos. He reported having a dry cough and losing 10 pounds over 3-6 months when he saw his healthcare provider. Besides his presenting symptoms, a review of his other systems revealed nothing noteworthy. As a result of his significant smoking history, his provider ordered a low-dose chest CT, which revealed two 1.6 cm and 1.2 cm spiculated nodules in the right upper lobe and an enlarged station 4R lymph node. The CT/PET revealed increased uptake in the pulmonary nodules, station 4R lymph node, and the gastroesophageal junction [Figures 1 A-C]. A contrast-enhanced CT scan of the abdomen and pelvis revealed a 3.7 cm mass in the right kidney [Figure 1 D]. A biopsy of the station 4R lymph node revealed large columnar cells with gland formation with positive stains

Contact Creticus Marak, MD, Department of Medicine, Pulmonary and Critical Care Medicine, Northeastern Health System, Tahlequah, USA.

for TTF-1 and Napsin A consistent with adenocarcinoma of the lung [Figure 2]. An upper gastrointestinal endoscopy revealed an esophageal mass encompassing half its diameter and extending approximately 5 cm in the lower esophagus; biopsy revealed invasive moderately differentiated esophageal adenocarcinoma with intestinal metaplasia consistent with Barrett's esophagitis [Figure 3]. A surgical oncologist offered him surgery for the renal mass, which he declined. However, he agreed to undergo a percutaneous kidney biopsy, which revealed clear cell neoplasm with positive stains for pan-cytokeratin and PAX8 consistent with clear cell renal cell carcinoma [Figure 4]. After evaluations by the medical and radiation oncologists, his lung cancer was staged as T3N2M0, and he was started on concurrent platinum-based chemoradiotherapy in October 2021. He was then placed on durvalumab for maintenance. His esophageal cancer was staged T2N0M0, and radiation treatment was started simultaneously with the treatment for lung cancer. His most recent office visit was in December 2022; he was doing well with no significant cancer-specific symptoms. He was offered surgery again for renal cell carcinoma, but he refused.

Discussion

Approximately 1.7% of patients with newly diagnosed cancer will eventually be diagnosed with more primary tumors [6]. Metachronous tumors are 2.7 times more common than synchronous [6,7]. While two synchronous tumors are uncommon, having a third synchronous malignancy is considered rare [8]. Since the data on multiple primary tumors has only increased recently, it is hard to say whether this is due to increased exposure to unknown carcinogens, increased awareness of the disease entity, technological advances that have improved diagnostic and staging workups, improved treatment of cancer patients, improved survival rates, or better monitoring.

Males are more likely than females to develop multiple primary malignant tumors, with a ratio of 2.3 to 1. Generally, patients with MPMTs are older than 50, on average around 62 years old [8]. The commonest histologic types for the first, second and third cancers are adenocarcinomas followed by squamous cell carcinomas [8]. The commonest site of involvement is the gastrointestinal tract followed by lungs, head and neck, urogenital system and breasts [8]. Considering MPMTs in older men with newly diagnosed cancer with multiple organ involvement is important. Patients with MPMTs usually present with nonspecific symptoms without specific signs or symptoms indicating cancer in a particular organ system; for instance, coughing and hemoptysis with lung cancer and gastrointestinal bleeding or bowel obstruction with colon cancer. Many synchronous tumors are discovered accidently during surgery or on the radiographic staging of the index cancer, as in our case.

Interestingly, the occurrence of MPMTs varies by region. In developed countries like the US, MPMTs are typically found in the digestive system, particularly the colon. Other countries have different tumor localizations, with higher incidences of breast, nasopharyngeal, gastric, and esophageal cancers in China, skin cancers in Turkey, and gastric and colorectal cancers in Japan [9]. Genetics and environmental factors like diet and occupational exposure may be responsible for these differences. It has been shown that some cancers tend to occur more frequently in the presence of others [9]. For example, older women with breast or melanoma are more likely to suffer from head, neck, or bladder cancers; and patients with head and neck cancers are more likely to develop lung and esophageal cancers [9,12]. Whether this results from exposure to common carcinogens, genetic abnormalities, improved diagnostic abilities, and treatment options or from providing older people with better access to healthcare remains to be determined.

Metachronous tumors usually have identifiable risk factors. Most patients have prior chemo, radiation, or both treatment history and generally live longer with more effective treatment. However, the risks for synchronous tumors are much less understood except for independent risk factors for each cancer, like smoking in our case. Despite theories like "field cancerization" or genetic or embryological abnormalities (BRCA, TP53, CHEK 1, and CCND1 mutations), no direct associations have been identified to link the development of synchronous primary tumors [8-11]. Our patient did not have a personal or family history of cancer or genetic abnormalities; smoking was the only identifiable risk factor for all three cancers.

For clinicians, managing patients with MPMTs can be very challenging. There are no well-defined treatment algorithms for managing multiple tumors due to a lack of controlled studies. A multidisciplinary approach is suggested to address each tumor separately [8]. As in our case, simultaneous treatment of all primary tumors may be an option but would increase adverse effects and complications. Eventually, the prognosis will depend on the tumor's histology and stage, with the worst one resulting in the worse outcome [9-11].

Our patient had multiple primary malignancies involving the lung, esophagus, and kidney. Our literature search identified only twenty-seven reported cases of triple synchronous malignancies with malignancy involving either the kidneys, esophagus, or lungs (Table 1). Only three of those twenty-seven cases (11%) had two of the three malignancies our patient had, and none of the reported cases had all three (lung, esophageal, and kidney).

Conclusion

Synchronous tumors are rare and pose diagnostic and treatment challenges. It is important to consider synchronous tumors in cancer patients with multiple organ involvement instead of assuming that the disease is caused by metastasis since a tumor's prognosis depends on its stage. Most patients with MPMTs present with nonspecific symptoms; in our patient, besides the chronic cough and weight loss, he had no cancer-specific symptoms. We could not identify which of the three cancers was the index cancer because he presented with three cancers simultaneously. Smoking was the only identified risk factor for all three cancers. This case report is intended to raise awareness of synchronous tumors in cancer patients with multiple organ involvement and contribute to the growing literature on triple synchronous tumors.

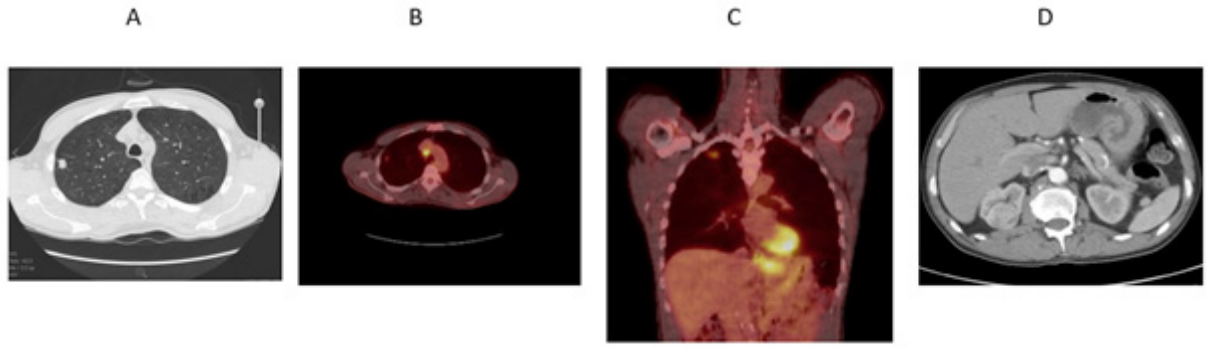

Figure 1: (A) CT showing a right upper lobe pulmonary nodule (B) CT PET showing an avid nodule and a station 4R lymph node (C) CT PET showing an increased uptake at gastroesophageal junction (D) CT showing mass in the right kidney.

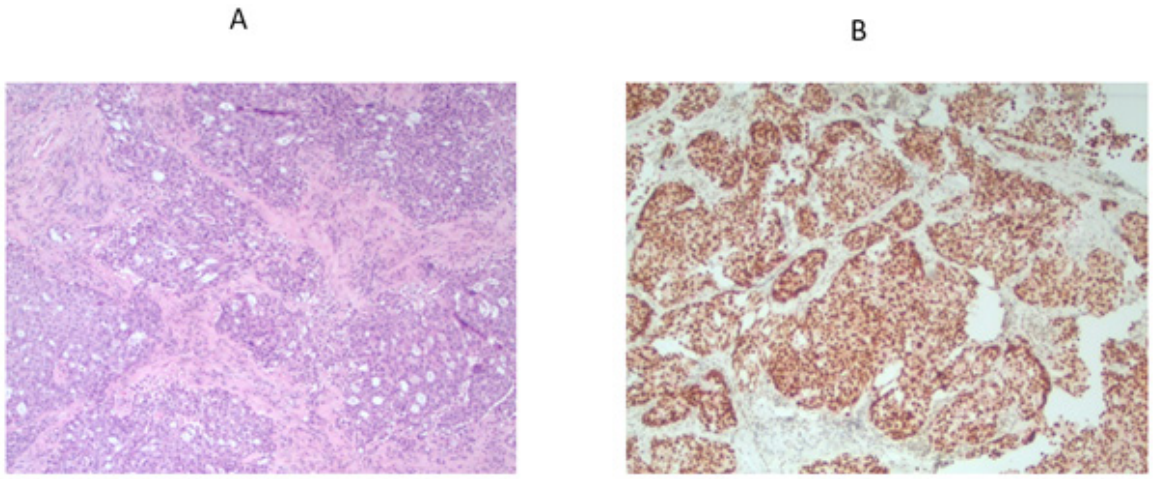

Figure 2: (A) Lymph node biopsy showing adenocarcinoma (B) IHC with positive staining for TTF1 and Napsin A.

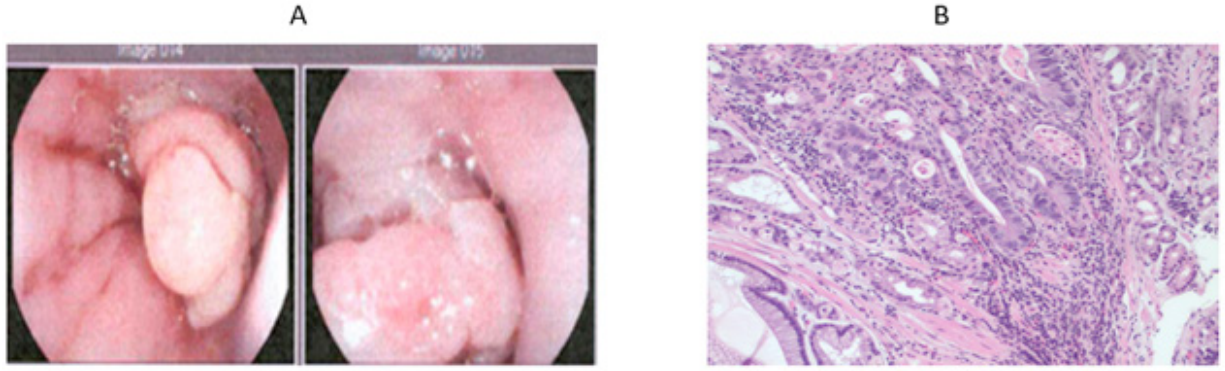

Figure 3: (A) EGD revealing an esophageal mass (B) H&E showing an esophageal adenocarcinoma.

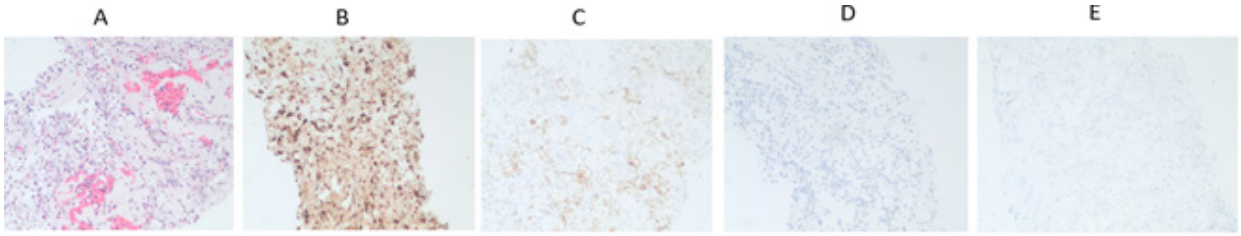

Figure 4: (A) Clear Cell RCC (B) IHC PAX * (C) IHC Ae1-AE3 (D) IHC CK7 (E) IHC CK 20.

Table 1: Reported Cases of Triple Synchronous Malignancies with either Lung, Esophageal or Renal involvement.

Author	Year	Age	Combination of Sync. Malignancies
Haibach et al. [13]	1984	NA	TC, RCC, CC
Jung-Legg et al. [14]	1986	49 M	LC, LC, LC,
Badiali et al. [15]	1987	63 M	LC, LC, LC
Burn et al. [16]	2002	57 M	LC, LC, LC
Froio et al. [17]	2008	59 M	LC, LC, LC
Jeon et al. [18]	2008	74 M	EC, HNC, LC
Ma et al. [19]	2010	75 M	LC, LC, LC
Ito et al. [20]	2012	78 F	LC, LC, LC
Zardo et al. [21]	2014	72 F	LC, LC, LC
Yoon et al. [22]	2014	72 M	LC, LC, LC
Ma et al. [23]	2014	35 F	TC, RCC, KC
Oh et al. [24]	2015	50 M	TC, RCC, GC
Jin et al. [25]	2015	66 F	BC, LC, LC
Testori et al. [7]	2015	66M	HNC, LC, CC, PC
Song et al. [26]	2016	63 F	EC, LC, HNC
Mendez et al. [27]	2016	60 F	EndC, RCC, CC
Doi et al. [28]	2017	74 F	LC, LC, LC
Kashif et al.[29]	2017	63 M	LC, LC, LC
Takada et al. [30]	2017	71 F	BC, LC, CC
Peng et al. [31]	2018	32 F	RCC, TC, LC
Peng et al. [32]	2019	58 M	TC, CC, RCC
Zhang et al. [33]	2019	81 M	LC, PC, BlC
Koyama et al. [34]	2020	64 M	LC, LC, LC
Li et al. [35]	2020	66 M	EC, LC, HCC
Kurose et al. [36]	2020	78 M	RCC, BlC, PC
Zhan et al. [37]	2021	70 M	EC, GC, CC
Mita et al. [10]	2022	59 M	PanC, EC, LC
Bannon et al. (Our Case)	2023	61 M	LC, EC, RCC

BC: Breast Cancer, BlC: Bladder Cancer, CC: Colon Cancer, EC: Esophageal Cancer; GC: Gastric Cancer, HNC: Head and Neck Cancer, HCC: Hepatocellular Carcinoma; KC: Kidney Cancer (Non RCC), RCC: Renal Cell Carcinoma, TC: Thyroid Cancer, PC: Prostate Cancer; PanC: Pancreatic cancer; EndC: Endometrial Cancer;

Acknowledgements

With great pleasure, we thank the medical and radiation oncology departments at the Northeastern Health System for providing excellent care to this patient.

References

1. Billroth T. Reimer G. Die allgemeine chirurgische pathologie und therapie. 51 Vorlesungen-Ein Handbuch fur Studierende und Artze, 14. Berlin: Auflage. 1889; 908.
2. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. Am J Cancer. 1932; 16: 1358-1414.
3. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open. 2017; 2(2): e000172.
4. Lv M, Zhang X, Shen Y, Wang F, Yang J, et al. Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. Medicine (Baltimore). 2017; 96(17): e6799.
5. Ghaed MA, Jahanshahi F, Maleki F. The First Report of Triple Advanced Synchronous Cancer: Bladder Transitional Cell Carcinoma and Clinically Silent Adenocarcinoma of Prostate and Colon. Int Med Case Rep J. 2019; 12: 373-377.
6. Irimie A, Achimas-Cadariu P, Burz C, Puscas E. Multiple primary malignancies--epidemiological analysis at a single tertiary institution. J Gastrointestin Liver Dis. 2010; 19(1): 69-73.
7. Testori A, Cioffi U, De Simone M, Bini F, Vaghi A, et al. Multiple primary synchronous malignant tumors. BMC Res Notes. 2015; 8: 730.
8. Zhai C, Cai Y, Lou F, Liu Z, Xie J, et al. Multiple Primary Malignant Tumors - A Clinical Analysis of 15,321 Patients with Malignancies at a Single Center in China. J Cancer. 2018; 9(16): 2795-2801.
9. Xu LL, Gu KS. Clinical retrospective analysis of cases with multiple primary malignant neoplasms. Genet Mol Res. 2014; 13(4): 9271-9284.
10. Mita J, Iguchi T, Iseda N, Takada K, Hirose K, et al. A case of successful conversion surgery for locally advanced pancreatic cancer with synchronous triple cancer of the lung and esophagus: a case report. Surg Case Rep. 2022; 8(1): 19.
11. Pastore AL, Palleschi G, Leto A, Silvestri L, Porta N, et al. A novel combination of triple metachronous malignancies of the kidney, oropharynx and prostate: A case report. Oncol Lett. 2015; 10(2): 917-920.
12. Coyte A, Morrison DS, McLoone P. Second primary cancer risk - the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer. 2014; 14: 272.

13. Haibach H, Rosenholtz M. Synchronous Thyroid, Renal, and Duodenal Carcinomas. Arch Pathol Lab Med. 1984; 108(4): 272-274.

14. Jung-Legg Y, Mcgowan SE, Sweeney KG, Zitzman JL, Pugatch RD. Synchronous Triple Malignant Tumors of the Lung: A Case Report of Bronchial Carcinoid, Small Cell Carcinoma, and Adenocarcinoma of the Right Lung. Am J Clin Pathol. 1986; 85(1): 96-101.

15. Badiali P, Alloisio M, Lombardi L. Synchronous Triple Carcinoma of the Lung in One Patient. Tumori. 1987; 73(5): 525-529.

16. Burn S, Paparelli C, Sinnona N, Venuti V. Synchronous Lung Cancer; Clinical Case of Triple Lung Carcinoma. G Chir. 2002; 23(1): 43-44.

17. Froio E, D'Adda T, Fellegara G, Ampollini L, Carbognani P, et al. Three different synchronous primary lung tumors: a case report with extensive genetic analysis and review of the literature. Lung Cancer. 2008; 59(3): 395-402.

18. Jeon SY, Ahn SH, Kim CH, Lim SM, Koh JS, et al. Esophageal and Laryngeal Cancer Incidentally Found on [18 F] Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography During the Staging Workup for Lung Cancer. Clin Lung Cancer. 2008; 9(4): 230-231.

19. Ma ESK, Cheng PNM, Wong CLP, Yim APC. Synchronous primary lung cancer and epidermal growth factor receptor mutation. Ann Thorac Surg. 2010; 90(3): e38-39.

20. Ito T, Kawasaki N, Kinoshita M, Inada H, Tei S, et al. Triple Synchronous Primary Lung Carcinomas in the Same Lobe; Report of a case. Kyobu Geka. 2012; 65(9): 832-835.

21. Zardo P, Krüer T, Schiffmann S, Freermann S, Fischer S. Triple Synchronous Primary Lung Cancer. Asian Cardiovasc Thorac Ann. 2014; 22(7): 865-868.

22. Yoon HJ, Lee HY, Han J, Choi Y-L. Synchronous Triple Primary Lung Cancers: A Case Report. Korean J Radiol. 2014; 22(7): 865-868.

23. Ma J, Du J, Zhang Z, Wang H, Wang J. Synchronous primary triple carcinoma of thyroid and kidney accompanied by solitary fibrous tumor of the kidney: a unique case report. Int J Clin Exp Pathol. 2014; 7(7): 4268-4273.

24. Oh SJ, Bae DS, Suh BJ. Synchronous triple primary cancers occurring in the stomach, kidney, and thyroid. Ann Surg Treat Res. 2015; 88(6): 345-348.

25. Jin CJ, Mei X, Falkson CB. A case of synchronous breast and bilateral lung cancers: literature review and considerations for radiation treatment planning. BJR Case Rep. 2017; 3(1): 20150464.

26. Song X, Shen H, Li J, Wang F. Minimally Invasive resection of synchronous triple primary tumors of the esophagus, lung, and thymus: A case report. Int J Surg Case Rep. 2016; 29: 59-62.

27. Mendez LE, Atlass J. Triple synchronous primary malignancies of the colon, endometrium and kidney in a patient with Lynch syndrome treated via minimally invasive techniques. Gynecol Oncol Rep. 2016; 17: 29-32.

28. Doi T, Sakamoto T. Synchronous Triple Primary Lung Adenocarcinomas, one of which showing a thin-walled cavity nodule; report of a case. Kyobu Geka. 2017; 70(3): 227-230.

29. Kashif M, Ayyadurai P, Thanha L, Khaja M. Triple Synchronous Primary Lung Cancer: A Case Report and Review of the Literature. J Med Case Rep. 2017; 11(1): 245.

30. Takada K, Hashiwagi S, Amano R, Goto W, Asano Y, et al. A Case of Synchronous Triple Cancer of the Breast, Duodenal, and Lung. Gan To Kagaku Ryoho. 2017; 44(12): 1074-1076.

31. Peng L, Zeng Z, Teng X, Chen Z, Lin L, et al. Genomic profiling of synchronous triple primary tumors of the lung, thyroid and kidney in a young female patient: A case report. Oncol Lett. 2018; 16(5): 6089-6094.

32. Peng C, Li Z, Gao H, Zou X, Wang X, et al. Synchronous primary sigmoid colon cancer and primary thyroid cancer followed by a malignant tumor of the kidney: Case report of multiple primary cancer and review of the literature. Oncol Lett. 2019; 17(2): 2479-2484.

33. Zhang Y, Ge Y, Wu X, Liu S. Clinical Treatment of Advanced Synchronous Triple Primary Malignancies: Comprehensive Treatment Based on Targeted Therapy. Onco Targets Ther. 2019; 12: 2421-2430.

34. Koyama T, Shimizu K, Uehara T, Matsuoka S, Takeda T, et al. Synchronous Triple Primary Lung Cancer with Three Different Histological Subtypes in the Same Lobe: A Case Report. Thorac Cancer. 2020; 12(5): 711-714.

35. Li D, Zhou P, Yang J, Wang Y, Yu M. Whole-exome sequencing in a patient with synchronous triple primary malignancies involving lung cancer: a case report. Precis Clin Med. 2020; 3(4): 306-310.

36. Kurose H, Ueda K, Nakiri M, Matsuo M, Suekane S, et al. Synchronous primary triple urogenital malignant tumors of kidney, prostate and bladder. Urol Case Rep. 2020; 33: 101277.

37. Zhan X, He L, Song K, Cao S, Meng E, et al. Case Report: Triple Primary Malignant tumors of the Esophagus, Stomach, and Colon in a Patient with Genetic Analysis. Front Genet. 2021; 12: 676497.