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Case Report

Triple Synchronous Malignancies of the Stomach, Bladder and Thyroid in a Previously Treated Prostate Cancer Patient: A Case Report

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Abstract

Cancers that develop within six months of the first primary cancer are referred to as synchronous malignancies. These malignancies are difficult to diagnose and treat, with treatment primarily based on case reports.

We report here the case of a 51-year-old male with prior history of prostate cancer who presented with haematuria to the general practice. A CT pyelogram showed left bladder wall lesion that was further investigated with cystoscopy and biopsy confirmed as muscle-invasive urothelial carcinoma. Incidentally, two perigastric nodes and hepatic lesions were noted on CT. FDG-PET revealed high-grade uptake in the right lobe of thyroid gland and cervical nodes that was biopsy proven as papillary thyroid carcinoma. Subsequently, gastroscopy and a biopsy of the gastric lesion confirmed a gastric neuroendocrine tumour. The patient underwent chemoradiotherapy, total thyroidectomy, and commenced somatostatin analogue for treatment of urothelial carcinoma, papillary thyroid carcinoma, and neuroendocrine tumour, respectively.

The diagnosis and treatment of synchronous malignancies is complex. A multidisciplinary team approach is required to improve treatment outcomes.

Keywords

synchronous malidnancies, neuroendocrine cancer, thyroid cancer, bladder cancer, case report

INTRODUCTION

Synchronous malignancies (SM) refer to two or more independent primary cancers where the second, third, and subsequent cancer arise within 6 months of the primary cancer.[1] In regard to its prevalence, the frequency of SM ranges from 2 to 17%.[2-4] However, in recent years, the frequency of SM is rising owing to better diagnostic tests and improved cancer screening.[5] There are several identifiable risk factors for SM, including but not limited to inherited predisposition to cancer, environmental exposures, index cancer diagnosed at an early age, and a positive family history of cancer.[6] Diagnosis of SM can be challenging as it first requires ruling out metastases from the first primary cancer. Other factors which make the diagnosis particularly difficult are low differentiation, high similarity in histology or inaccessibility of the tumour tissue being investigated. In clinical practice, it is crucial to perform adequate and

relevant investigations as incorrect diagnosis has implications on choice of therapy.

Some SM are known to occur in specific types of cancers as a consequence of inheritance of cancer predisposition syndrome.[7-9] Synchronous breast and ovarian cancer; prostate cancer, and pancreatic cancer or melanoma are prominent findings in hereditary breast ovarian cancer syndrome.[7] Synchronous colon and endometrial cancer prompt to the presence of Lynch syndrome.[7] However, some synchronous malignancies are random, as in our case. We present a unique case of a 51-year-old male who developed synchronous malignancies of high grade gastric neuroendocrine tumour (NET), papillary thyroid cancer (PTC), and urothelial carcinoma (UC) of the bladder. Here, we also provide an overview of the approach to diagnosis and management of SM, with particular reference to our case.

CASE DESCRIPTION

A 51-year-old male of Italian ethnicity presented to the general practice with a 4-day history of haematuria and lower urinary tract symptoms, including dysuria and increased urinary frequency. He was otherwise well, with no abdominal pain, nausea, vomiting, bowel habit alterations, weight loss, fever, or night sweats. A review of other systems was unremarkable. He had a prior history of locally advanced prostate cancer diagnosed at age 42, for which he underwent a robotic prostatectomy and had since then been in remission. The patient works as a fire system tester; however, no significant exposure to carcinogenic chemicals was noted. He had a 30 pack-year smoking history, no other significant co-morbidities, and occasionally drinks alcohol. In terms of family history, the patient's mother had breast cancer and brother had prostate cancer, both diagnosed above the age of 50.

A CT pyelogram showed a hepatic lesion and a left bladder wall lesion that was further investigated by the Urology team one month later with a cystoscopy and biopsy of the lesion, which was histologically confirmed as T2 high-grade muscle-invasive UC with lymphovascular invasion. A CT scan incidentally noted two perigastric lymph nodes measuring 1 cm each, along with hepatic lesions. A fluorodeoxyglucose (FDG)-PET scan was subsequently performed, revealing high-grade uptake in the upper pole of the right lobe of the thyroid gland, highly suspicious of another primary cancer ***(Fig. 1)****. The perigastric lymph nodes and hepatic lesions were not FDG avid. Further characterisation of the hepatic lesions using MRI revealed multifocal lesions in segment II and III of the liver, suspicious of metastases. An ultrasound of the thyroid was performed, showing 39×21×18 mm solid hypoechoic, well-defined coarse calcified upper right thyroid nodule, and a right level 4 lymph node microcalcification lesion measuring 23×14×22 mm. Referral was made to the Endocrinology Surgical team for fine needle aspiration of the right thyroid nodule, along with the surrounding level 4 lymph node which demonstrated PTC. With regard to the liver lesions found on MRI, the lesions were further investigated with an ultrasound-guided biopsy, which was abandoned as it was considered unsafe due to the position of the lesion adjacent to the confluence of the hepatic vein and the inferior vena cava. A gastroscopy was also performed showing a 25-mm excavated lesion (Paris 0-3) along the lesser curve, which was histologically confirmed as grade 3 gastric NET – Ki-67 index of 22%, synaptophysin and CD56 positive, chromogranin negative* ***(Figs 2, 3)****. A gallium octreotide PET scan was also ordered, showing significant uptake in the primary gastric mass as well as a segment II and IV liver metastasis, consistent with metastatic neuroendocrine tumour. It also*

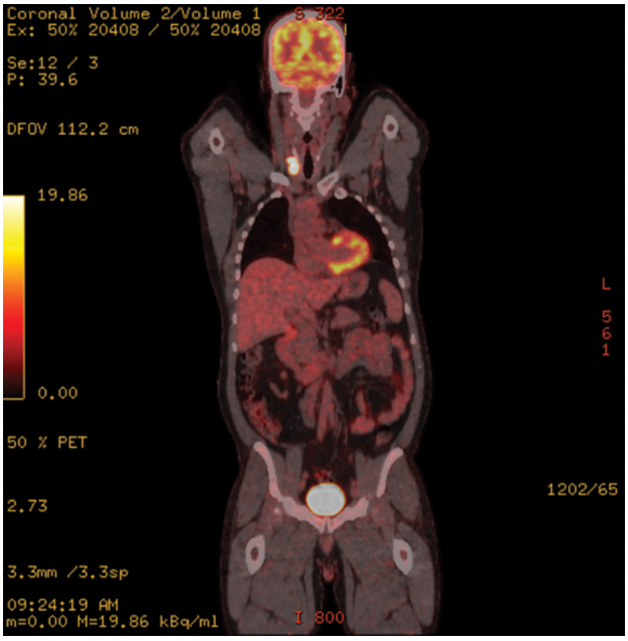

Figure 1. FDG-PET scan revealing high-grade uptake in the upper pole of right lobe of thyroid gland.

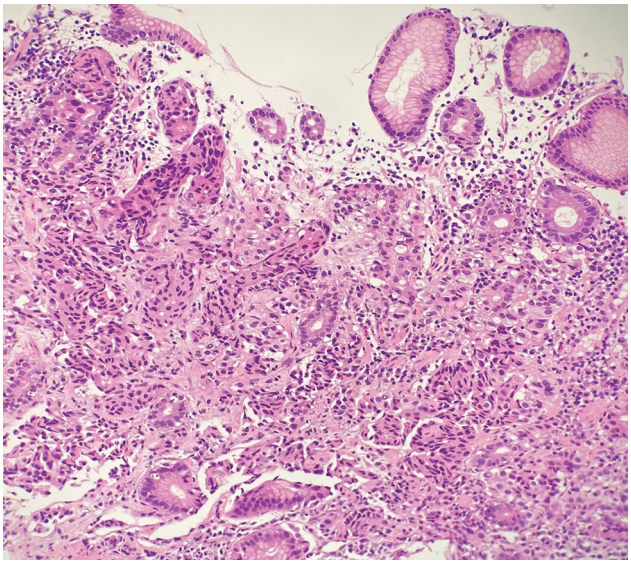

Figure 2. Neuroendocrine tumour grade 3 of primary gastrointestinal tract origin. H&E stained sections depicting tumour cells with stippled chromatin and lack of mitotic activity.

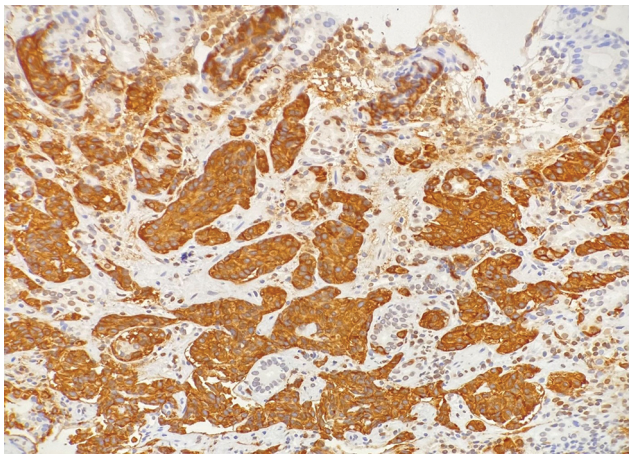

Figure 3. Neuroendocrine tumour grade 3 of primary gastrointestinal tract origin. Synaptophysin immunostain showing diffuse cytoplasmic positivity in tumour cells.

showed a hot spot in the tail of pancreas suggestive of perhaps another primary NET ***(Fig. 4)****.*

The patient was discussed in both urology and upper gastrointestinal multidisciplinary team (MDT) meetings at a tertiary hospital and the consensus was to proceed with curative-intent radical chemoradiotherapy with 5-flurouracil and mitomycin for UC, total thyroidectomy with right modified radical neck dissection for his PTC and commence a somatostatin analogue (SSA) for treatment of his NET with consideration of surgery down the track if the tumour responds positively to SSA such that R0 resection can be achieved or trial of peptide receptor radionuclide therapy (PRRT) in the event of lanreotide failure.

Upon completion of radical chemoradiotherapy for urothelial carcinoma of the bladder, the patient had radiological and clinical complete response on FDG-PET and three months later remained in remission. Gastric NET was complicated by perforation of the tumour which was managed conservatively with intravenous antibiotics. Having completed three cycles of lanreotide injection, the patient demonstrated a partial treatment response with reduction in size of gastric, liver, and pancreas lesion on gallium octreotide PET scan. Therefore, surgery may be offered in the future as planned if patient is keen. Finally, with regards to his PTC, upon undergoing a total thyroidectomy, the cancer was found to be locally advanced with lymphovascular invasion (T2N1bM0, stage I), prompting referral to the Nuclear Medicine Team for adjuvant radioactive iodine therapy. Thyroid surgery was also complicated by a mild neck seroma which did not require any surgical intervention.

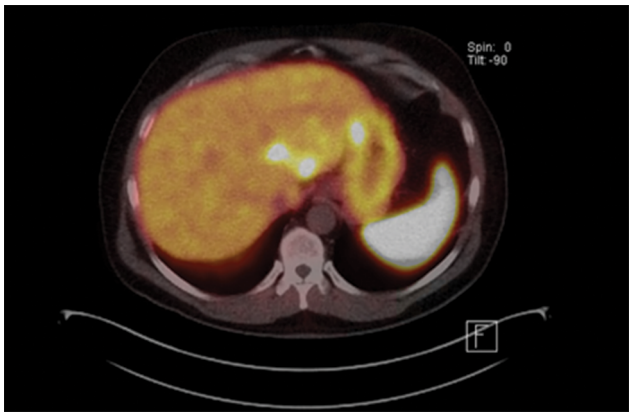

Figure 4. Gallium octreotide PET scan showing significant uptake in the primary gastric mass as well as a segment II and IV liver metastasis, consistent with metastatic neuroendocrine tumour.

Nine months since the diagnosis of his SM, the patient remained well while maintaining a good quality of life. With the support of his friends and partner, he coped well with the complex treatment of his SM and is adamant that he would pursue all recommended treatment in the future intended to prolong life. His cancer surveillance regimen include 3 monthly FDG-PET scan for surveillance of his bladder cancer, 3 monthly gallium octreotide PET scan for his NET, and 6 monthly ultrasound of the thyroid for his thyroid cancer. He has also been tested by Genetic Services of Western Australia for genetic abnormalities or familial syndromes and awaiting results.

DISCUSSION

We presented a unique case of a 51-year-old male with SM of gastric NET, PTC, and UC of the bladder. To the best of our knowledge, this is the first case of its kind to be reported in the literature, with no notable cancer syndrome plausibly explaining this spectrum of malignancies. While SM of NET and other primary malignancies used to be regarded as an exotic event, a recent study by Parra-Medina et al.[10] revealed that it was not uncommon for NET to exist synchronously with other malignancies. The systematic review of case reports identified that the most common types of SM associated with NET were adenocarcinoma (49.4%), followed by gastrointestinal stromal tumours (13.5%), other NETs in different gastrointestinal segments (7.9%), lymphoma (6.8%), and squamous cell carcinoma (4.5%).[10] Number of theories have been postulated on SM involving NET including the presence of a common carcinogenic effect, including the release of growth factors and secretory peptides by NET in a paracrine and autocrine manner that promote the development of NET and other malignancies and common stem cell lineage that undergoes similar genetic mutations, giving rise to SM.[11-13]

In recent years, the availability of sophisticated imaging methods such as PET-CT scans and whole-body MRI implies that it is not uncommon for incidental lesions that would have not been picked up by conventional CT scan to be detected. In a series of 200 patients with oesophageal cancer who had PET-CT scan, 17% of patients had SM with cancers in various organs from stomach, colon to lung.[14] Hence, it is relatively common for SM to be diagnosed on imaging for cancer staging, as in our case. Some clinical features should prompt consideration of a SM – metastasis of primary tumour to an atypical site such as in our case, a thyroid lesion was detected on staging scans for bladder

UC; differential standard uptake value (SUV) of suspected lesions on PET-CT; high tumour burden in the setting of low tumour marker load; haematological malignancy in the setting of prior history of chemotherapy.[15] Suspicion of SM should be confirmed by histological confirmation of the suspicious lesion, especially in patients desiring active treatment, with comparison made to the primary tissue.[15]

Treatment of patients with SM is complex and clinicians often encounter a therapeutic dilemma. Discussion in a multidisciplinary team involving at least medical oncologists, surgeons, radiation oncologists, radiologists, and pathologists is required to maximise treatment success and outcomes.[15] Due to the complexity of SM, patients should be informed of the uncertainty of prognosis, therapeutic challenges, and the treatment needs to be adapted to align with patients' goals. Patients should be informed that treatment experience for SM is limited and based on case reports/series rather than randomised controlled trials. In localised disease, treatment strategy could involve surgery or chemoradiotherapy, whereas in advanced disease, strategy could involve multimodality therapy – combination of surgery, systemic therapy, and radiotherapy.[15] In deciding treatment strategy, one must determine the most significant tumour in terms of prognosis and whether treatment is curative or palliative, followed by the strategy of local versus systemic therapy or a combination of the two. Provided that systemic therapy is required, one must attempt to ascertain the best combination regimen that is active against both malignancies while also considering drug interactions such as cytochrome P450 interactions.[15] In this era of personalised medicine, tumour profiling should also be performed, when resources permit, to determine patients' eligibility for targeted therapy and immunotherapy, which would maximise treatment success.

In our case, following the diagnosis of SM, the patient was adamant that he wanted to pursue treatment with curative intent. Following the diagnosis of muscle invasive bladder cancer, the patient elected for chemoradiotherapy with curative intent. The patient completed concurrent chemoradiotherapy with mitomycin and 5-flurouracil and 55 Gy in 20 fractions of definitive radiotherapy and was declared in remission. A multidisciplinary team (MDT) convened for discussion of the patient's thyroid cancer and NET came to a consensus that the patient should proceed with a curative treatment for thyroid cancer - total thyroidectomy with right modified radical neck dissection - and commence lanreotide injection for his NET, which the patient agreed to. The decision for the latter was based on the fact that the patient presented with advanced disease, making it impossible to achieve R0 resection, and limited evidence of the role of debulking surgery for NET relative to treatment with lanreotide.[16,17] The MDT also agreed on monitoring the progress of the disease post commencing lanreotide, with consideration of peptide receptor radionuclide therapy (PRRT) if lanreotide fails given increasing evidence of success of PRRT in NET management.[18,19]

Limitations on this case report include the unavailability of genomic data at the time of writing to explain the spectrum of SM and the short follow-up time of the patient since first diagnosed. However, our report provides valuable insight into the management of a rare spectrum of SM – the first of its kind to be reported in the literature.

CONCLUSIONS

In conclusion, SM can be difficult to diagnose and treat. A multidisciplinary team management approach should be adopted to optimise treatment for patients with SM, with treatment tailored to align with patients' goals. As patients with SM are generally excluded from clinical trials, it is unlikely that randomized control trials will be conducted in the future to inform best practice for management of SM. However, with the advancement of tumour profiling, tumour samples from the SM should be genomically profiled to optimise treatment strategy and improve patient outcomes.

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Competing Interests

The authors have declared that no competing interests exist.

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Тройные синхронные злокачественные новообразования желудка, мочевого пузыря и щитовидной железы у ранее леченного пациента с раком простаты: клинический случай

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Резюме

Рак, который развивается в течение шести месяцев после первого первичного рака, называется синхронным злокачественным новообразованием. Эти злокачественные новообразования трудно диагностировать и лечить, при этом лечение в основном основано на отчётах о случаях заболевания.

Мы сообщаем здесь случай 51-летнего мужчины с предшествующим анамнезом рака предстательной железы, который обратился с гематурией в общую практику. КТ-пиелограмма показала поражение левой стенки мочевого пузыря, которое было дополнительно исследовано с помощью цистоскопии и биопсии, подтверждённой как мышечно-инвазивная уротелиальная карцинома. Кстати, на КТ были отмечены два перигастральных узла и поражение печени. ФДГ-ПЭТ выявила высокую степень поглощения в правой доле щитовидной железы и шейных лимфатических узлах, что было подтверждено биопсией как папиллярная карцинома щитовидной железы. Впоследствии гастроскопия и биопсия поражённого участка желудка подтвердили нейроэндокринную опухоль желудка. Пациенту была проведена химиолучевая терапия, тотальная тиреоидэктомия и назначен аналог соматостатина для лечения уротелиальной карциномы, папиллярной карциномы щитовидной железы и нейроэндокринной опухоли соответственно.

Диагностика и лечение синхронных злокачественных новообразований сложны. Для улучшения результатов лечения требуется междисциплинарный командный подход.

Ключевые слова

синхронные злокачественные новообразования, нейроэндокринный рак, рак щитовидной железы, рак мочевого пузыря, клинический случай