CASE REPORT

Triple synchronous primary malignancies: a rare occurrence

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SUMMARY

Triple synchronous primary malignant neoplasms are rare. The exact aetiology is unknown; however, risk factors include older age, family history, genetic aberrations, prolonged exposure to carcinogens and smoking. We describe a previously healthy 48-year-old woman who presented with abdominal pain and a palpable abdominal mass. Imaging revealed a complex cystic, solid pelvic mass and another mass in the right upper quadrant. She received an extensive abdominal surgery including exploratory laparotomy, pelvic mass resection, total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, omentectomy and right adrenalectomy. During surgery, a mass in the distal sigmoid colon was noted and subsequent sigmoidectomy was performed. The surgical specimen revealed three different primary tumours with three different histologies, a granulosa cell tumour of the ovary, adrenocortical carcinoma and adenocarcinoma of the colon. She received six cycles of adjuvant chemotherapy for colon cancer with 5-fluorouracil, leucovorin and oxaliplatin and is currently living with no recurrence.

BACKGROUND

Multiple primary malignant neoplasms (MPMN) have been reported in the literature.^{1–14} MPMNs require each lesion to be malignant, have different pathology and metastatic disease has been ruled out.² Synchronous MPMNs are rare, especially more than two primary neoplasms.^{3–4, 6–8–12} The gastrointestinal tract, lungs and breasts have been the most common locations of synchronous MPMN.¹⁰ Few case reports have described triple synchronous primary neoplasms in three different organ systems. There have been no reports of synchronous ovarian, adrenal and colon cancers.

CASE PRESENTATION

A 48-year-old woman with no significant medical history presented with lower abdominal pain for 2 weeks duration. She stated it was 10/10 severity and described it as crampy. The pain radiated to her back and anterior legs. She also noticed some abdominal swelling and bloating. She denied any haematuria, hematochezia, melena, nausea, vomiting, diarrhoea or constipation. Her last bowel movement was 1 day prior and her last menses was 2 years prior. She had not had a colonoscopy and had not seen a physician in >10 years.

The patient denied any medical or surgical history. She also denied any alcohol, tobacco or recreational drug use in her lifetime. She had no history of exposures or contact with hazardous material. Family history was significant for a sister and mother with benign ovarian tumours and a father and maternal grandfather that was diagnosed with colon cancer. Her father was diagnosed at age 65 and passed away at age 80, and her maternal grandfather was also diagnosed later in life.

Physical exam revealed sinus tachycardia at 120 beats per minute and a soft abdomen with a large abdominal mass reaching to the umbilicus. She had mild suprapubic tenderness but no rebound or guarding. Laboratory data showed a mild leukocytosis, otherwise laboratory data including pregnancy test and urine analysis were unremarkable. CT scan of the abdomen and pelvis with intravenous contrast revealed a 13.2 cm mass in the right upper quadrant with inferomedial displacement of the right kidney and apparent displacement of the liver that presumably represented an adrenal mass as well as a complex cystic and solid mass within the pelvis measuring 15.8 cm transverse by 12.9 cm anterior-posterior by 18.0 cm in craniocaudal dimension that presumably represented an ovarian cancer (figure 1).

Further labs were obtained prior to resection. The adrenal gland was not metabolically active as 24 hours urine metanephrines and normetanephrines (145 µg/24 hours and 395 µg/24 hours), timed urine aldosterone (<0.11 µg/24 hours), free urine cortisol (25 µg/24 hours) and urine vanillylmandelic acid (4.0 mg/24 hours) were within normal limits. Plasma metanephrines and normetanephrines (35 and 119 pg/mL) were also within normal limits and serum cortisol was only slightly elevated at 23.1 µg/dL (table 1). CA-125 was within normal limits, 28.4 units/mL (table 2).

The patient first received an exploratory laparotomy, pelvic mass resection, total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy and omentectomy by gynecology (GYN) oncology and then urology performed a right radical adrenalectomy. During abdominal exploration, a mass in the distal sigmoid colon with some inflammation concerning malignancy was seen and thus general surgery performed a sigmoidectomy.

Pathology revealed that the left pelvic mass was a 19×18×14 cm granulosa cell tumour (figure 2). Pathological stage of this granulosa cell tumour was pT1a, pN0, pMx. Appropriate

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Figure 1 CT scan of the abdomen and pelvis with intravenous contrast revealed a 13.2 cm mass in the right upper quadrant with inferomedial displacement of the right kidney as well as apparent displacement of the liver (blue arrow) and a complex cystic and solid mass within the pelvis measuring 15.8 cm transverse by 12.9 cm anterior-posterior by 18.0 cm in craniocaudal dimension (red arrow).

immunohistochemistry stains were obtained to make the diagnosis including positive calretinin, positive vimentin, positive inhibin (figure 3), positive CD 99, focal positive AE1/AE3 and negative epithelial membrane antigen (EMA). Four right and four left pelvic lymph nodes were negative for metastasis. The right adrenal gland was well-circumscribed with the capsule intact, measured 17.5×12.4×9 cm and was determined to be an adrenocortical carcinoma (figure 4). Pathological stage was pT2, pNx, pMx. Immunohistochemical stains were negative for CD15, chromogranin and S100 and positive for calretinin, vimentin, inhibin, Melan-A (figure 5) and AE1/AE3. Finally, the sigmoid colon showed moderately differentiated adenocarcinoma (figure 6) with extension through the wall of the colon into the subserosal adipose tissue with 2/15 lymph nodes with adenocarcinoma. (figure 7) Pathological staging was pT3, pN1b, pMx. Immunohistochemistry for caudal type homeobox (CDX) 2 and CK20 is positive in adenocarcinoma of the colon.

CT chest with intravenous contrast was done to complete the staging work up and showed a 4 mm right upper lobe nodule that

Table 1 Urine and serum tests to assess metabolic activity of the adrenal glands

Metabolic tests	Reference range	Actual value
24 hours urine metanephrines	45–290 µg/24 hours	145 µg/24 hours
24 hours urine normetanephrines	82–500 µg/24 hours	395 µg/24 hours
Timed urine aldosterone	0.00–19.00 µg/24 hours	<0.11 µg/24 hours
Free urine cortisol	0–50 µg/24 hours	25 µg/24 hours
Urine vanillylmandelic acid	0.0–7.5 mg/24 hours	4.0 mg/24 hours
Plasma metanephrines	0–62 pg/mL	35 pg/mL
Plasma normetanephrines	0–145 pg/mL	119 pg/mL
Serum cortisol	3.1–22.4 µg/dL	23.1 µg/dL (H)

Table 2 Tumour marker trends from diagnosis to 1 year postop including carcinoembryonic antigen (CEA), CA-125, inhibin A and inhibin B

	bHCG	CEA (ng/mL)	CA-125 (units/mL)	Inhibin A (pg/mL)	Inhibin B (pg/mL)
Preop	Neg		28.4		
Three months postop		0.8			
Six months postop		2.1		0.9	<7.0
Nine months postop		1.5			
One year postop		1.2		0.7	<7.0

bHCG, beta-human chorionic gonadotropin.

was followed. Final staging of the three primary malignancies according to the American Joint Committee on Cancer tumour, node, metastases staging system revealed a stage IA granulosa cell tumour, a stage II adrenocortical carcinoma and a stage III adenocarcinoma of the colon. She was started on the modified 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) 6 regimen for her stage III adenocarcinoma of the colon and ultimately received 12 cycles. Follow-up CT chest/abdomen/pelvis showed stable scans and no evidence of recurrent disease and inhibin levels and carcinoembryonic antigen (CEA) remained within normal limits (table 2). Radiation oncology did not recommend adjuvant irradiation to any of the disease sites.

Given that the patient had three synchronous primary malignancies, genetic counselling was offered and performed. Counselling regarding risk for Lynch syndrome, Peutz-Jeghers syndrome and Li Fraumeni syndrome was discussed. The impact of genetic testing for other family members and screening and prevention strategies for unaffected family members was also discussed with the patient and the patient was going to contact her family. MYRIAD myRisk Hereditary Cancer results showed a mutation of the breast cancer 1 (BRCA1) gene. Other genes that were analysed and negative include adenomatous polyposis coli, ataxia telangiectasia mutated, BRCA1-associated RING domain protein, bone morphogenetic protein receptor, type IA, breast cancer 2 (BRCA2), BRCA1-interacting protein 1, cadherin-1, cyclin-dependent kinase 4, cyclin-dependent kinase inhibitor 2A, checkpoint kinase 2, epithelial cell adhesion molecule (large rearrangement only), MutL homolog 1, colon cancer, non-polyposis type 2, MutS protein homolog 2, mutS

Figure 2 H&E stain showing a granulosa cell tumour of the ovary showing characteristic Call-Exner bodies.

Figure 3 Positive immunohistochemistry staining for inhibin.

homolog 6, mutY DNA glycosylase, nibrin, partner and localiser of BRCA2, mismatch repair endonuclease PMS2, phosphatase and tensin homolog, RAD51 homolog C, DNA repair protein RAD51 homolog 4, mothers against decapentaplegic homolog 4, serine/threonine kinase 11 and tumour antigen p53. The findings of the BRCA1 mutation placed her at high risk for breast and ovarian cancer and elevated risk for pancreatic cancer. It was advised that the patient have close surveillance and monitoring for breast cancer.

Screening mammogram was performed and showed an ovoid mass in the posterior upper outer right breast, for which spot compression and ultrasound was recommended for further evaluation. She received a diagnostic mammogram that showed a solid, indeterminant mass within the posterior upper outer right breast. She received an ultrasound-guided biopsy of the right breast that showed breast tissue with stromal mucin containing rare atypical epithelial cells. There was concern for mucinous carcinoma. She received a bilateral mastectomy with right axillary sentinel node dissection. No malignancy was identified in the breasts or sentinel lymph nodes; however, the right breast did contain stromal mucin consistent with mucocele-like lesion.

OUTCOME AND FOLLOW-UP

Currently, >2 years since diagnosis, the patient is doing well and has no sites of recurrence or metastatic disease. She has completed her treatments with chemotherapy and is receiving

Figure 4 H&E stain, 60x power, showing adrenal cortical carcinoma.

Figure 5 Positive immunohistochemistry staining for Melan-A.

surveillance according to the National Comprehensive Cancer Network guidelines for colon cancer with history and physicals every 3 months for the first two years, CEA and imaging every 6 months. She received a recent colonoscopy that showed a normal colon with no evidence of recurrence and no polyps. In regards to her other primary cancers, she follows up with the respective physicians including urology and GYN oncology. She is also monitored with CT abdomen and pelvis every 6 months and inhibin levels every 3 months for the adrenal tumour and granulosa tumour, respectively.

DISCUSSION

MPMNs have been well described in the literature.^{1–14} Warren and Gates¹ describe the accepted criteria for the diagnosis of MPMNs: each lesion must be malignant, each lesion must have a different pathology and metastasis from prior primary malignancies must be ruled out. Demandante *et al*² state that the prevalence of MPMNs varies significantly between 0.73% and 16%.

The exact aetiology of MPMN is unknown.^{1–8} Risk factors associated with MPM include but are not limited to family history, immunological and genetic defects, prolonged exposure to carcinogens, smoking and radiation.^{3–8} A previous neoplasm or treatment for cancer with chemotherapy and radiotherapy are also risk factors for development of other tumours. Chong *et al*⁴ report age as the most important risk factor for MPMNs, and Demandante *et al*² calculate that 75%

Figure 6 H & E stain showing adenocarcinoma of the colon.

Figure 7 H&E stain of adenocarcinoma in a regional colon lymph node.

of patients who have multiple primary neoplasms are >50 years old. Sakellakis *et al*⁵ postulate that it may be the result of pure chance.

MPMNs can be synchronous or metachronous. Testori *et al*⁶ reported that synchronous lesions are seen less frequently than metachronous lesions, in a ratio of 1:2.7, respectively. Synchronous neoplasms are diagnosed at the time of diagnosis or within 6 months of diagnosis of primary tumour.^{6,8} They can occur either in a single organ or may involve multiple organs. Xu *et al*¹⁰ found that MPMNs occurred most commonly in the same organ in one system, in paired organs, or within the same organ, accounting for 45.3% of all cases. The most common locations of MPMN were the alimentary system, mammary gland and respiratory system.¹⁰ Because breast, ovarian and endometrial carcinoma are hormonally responsive, there is high probability of synchronous tumours at these sites.^{2,3,9,11} Prostate cancer has been frequently found incidentally in autopsies; thus, it is unclear if these cases should be considered true MPMNs.²

Few case reports have demonstrated the rarity of triple synchronous primary malignancies. Synchronous colorectal and adrenocortical carcinoma has been described twice in the literature. Economopoulou *et al*¹⁵ reported two case series in which patients with colon cancer underwent an adrenalectomy and one patient was found to have adrenocortical carcinoma. Karamurzin *et al*¹⁶ reported a patient with Lynch syndrome, who was found to have an adrenocortical carcinoma. Similarly, synchronous primary colon and ovarian tumours occur. It often presents with pseudomyxoma peritonei in association with mucinous neoplasms.¹² The synchronicity of a granulosa cell tumour of the ovary, adenocarcinoma of the colon and adrenocortical carcinoma has never been seen in the literature and further studies need to be done to find an association between these three cancers.

There are no guidelines regarding treatment of multiple synchronous neoplasms and therefore are difficult to treat. Yoshino *et al*¹³ reported that the prognosis of patients with multiple primary cancers can be determined independently by the stage of each cancer. Bae *et al*¹⁴ state that one of the most important factors when deciding the best treatment modality for patients with multiple primary cancer is the stage of the synchronous cancers. Synchronous primary cancers have much better survival rates than metastatic cases.^{12,13} Also,

synchronous primaries show better survival rates than single aggressive ovarian cancers.¹²

In summary, this is a rare case report of triple synchronous primary malignant neoplasms, and the first case of synchronous granulosa cell tumour of the ovary, adrenocortical carcinoma and adenocarcinoma of the colon. The presentation and course of this patient's care will be a useful adjunct to the current literature for determining treatment for patients with triple synchronous primary malignant neoplasms.

Learning points

- ▶ A multidisciplinary approach should be used for patients with multiple primary malignant neoplasms with plans formulated by teams of experts within their respective fields as no guidelines are established for patients with multiple synchronous primary malignancies.
- ▶ Patients should have close follow-up with all members of the multidisciplinary team to ensure the best outcome possible and hopefully increase survival.
- ▶ Patients who receive laparoscopic evaluation for gynaecological/genitourinary masses should always receive thorough examination of the colonic mucosa to evaluate for carcinoma.
- ▶ All patients with multiple primary malignant neoplasms should receive a comprehensive history including family history and exposure history to carcinogens, tobacco and radiation as well as genetic testing.
- ▶ Genetic testing and counselling is an important addition to the comprehensive work up for patients with multiple primary malignancies. If mutations are found, family members should be advised as they may wish to be tested or screened earlier.

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REFERENCES

- 1 Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and statistical study. *Am J Cancer* 1932;16:1358–414.
- 2 Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: case report and a comprehensive review of the literature. *Am J Clin Oncol* 2003;26:79–83.
- 3 Lee JS, Moon W, Park SJ, *et al*. Triple synchronous primary cancers of rectum, thyroid, and uterine cervix detected during the workup for hematochezia. *Intern Med* 2010;49:1745–7.
- 4 Chong VH, Idros A, Telisinghe PU. Triple synchronous gastrointestinal malignancies: a rare occurrence. *Singapore Med J* 2010;51:e 176–7.
- 5 Sakellakis M, Peroukides S, Iconomou G, *et al*. Multiple primary malignancies: a report of two cases. *Chin J Cancer Res* 2014;26:215–8.
- 6 Testori A, Cioffi U, De Simone M, *et al*. Multiple primary synchronous malignant tumors. *BMC Res Notes* 2015;8:730.
- 7 Slem A, Abu-Hijlil R, Abdelrahman F, *et al*. Eight primary malignancies: case report and review of literature. *Hematol Oncol Stem Cell Ther* 2011;4:185–7.
- 8 Meeks MW, Grace S, Chen Y, *et al*. Synchronous Quadruple primary neoplasms: colon adenocarcinoma, Collision tumor of neuroendocrine tumor and Schwann

- Cell Hamartoma and Sessile Serrated Adenoma of the appendix. *Anticancer Res* 2016;36:4307–11.
- 9 Kim JS, Chung CY, Park HC, *et al*. Synchronous quadruple primary tumors of thyroid, breast, pancreas, and stomach: a case report. *Anticancer Res* 2013;33:2135–8.
 - 10 Xu LL, Gu KS. Clinical retrospective analysis of cases with multiple primary malignant neoplasms. *Genet Mol Res* 2014;13:9271–84.
 - 11 Bezircioğlu I, Baloglu A, Karci L, *et al*. Synchronous renal oncocytoma, endometroid ovarian and endometrial carcinoma: a case report. *J Turkish-German Gynecol Assoc* 2009;10:43–6.
 - 12 Phupong V, Khemapech N, Triratanachai S. Triple synchronous primary cervical, endometrial and ovarian cancer with four different histologic patterns. *Arch Gynecol Obstet* 2007;276:655–8.
 - 13 Yoshino K, Asanuma F, Hanatani Y, *et al*. Multiple primary cancers in the stomach and another organ: frequency and the effects on prognosis. *Jpn J Clin Oncol* 1985;15(Suppl 1):183–90.
 - 14 Bae JS, Lee JH, Ryu KW, *et al*. Characteristics of synchronous cancers in gastric cancer patients. *Cancer Res Treat* 2006;38:25–9.
 - 15 Economopoulou P, Mountzios G, Kotsantis I, *et al*. Adrenal incidentalomas in cancer patients are not always "innocent": a case report and review of the literature. *Case Rep Med* 2013;2013:1–5.
 - 16 Karamurzin Y, Zeng Z, Stadler ZK, *et al*. Unusual DNA mismatch repair-deficient tumors in Lynch syndrome: a report of new cases and review of the literature. *Hum Pathol* 2012;43:1677–87.

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