

CASE REPORT

Quadruple Primary Malignancy of the Scalp, Colon, and Prostate in a Single Patient: A Unique Case Report and Review of Literature

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Abstract: Multiple primary malignancies are rare but early detection can be achieved with the advent of advanced imaging techniques. Diagnosis of all synchronous malignancy is vital for planning and favorable outcome. In this study, we present a case of synchronous triple primary malignancy consisting of squamous carcinoma scalp, adenocarcinoma prostate, and adenocarcinoma ascending colon with history of sigmoid colon cancer 11 years back. There were 12 possible treatment options and three alternative treatment sequences. Multidisciplinary tumor board team decided to begin the treatment with hormonal therapy (Enzalutamide/Leuprolide) for advanced metastatic prostate cancers. This was followed by simultaneous surgery consisting of wide excision of the right scalp lesion and right hemicolectomy. After a year of follow-up, patient remained disease progression free. This is the first quadruple malignancy case described in literature with the combination of scalp, prostate, and colon cancers as triple synchronous malignancy. Each cancer had its own diagnostic and treatment dilemma. Collectively, sequence of management of each cancer was also a predicament. Multidisciplinary management plays a pivotal role in the successful management of synchronous malignant tumors.

Keywords: Quadruple malignancy; Multidisciplinary approach; Dilemmas

1. Introduction

According to GLOBOCAN 2020, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020^[1]. However, with the improvement in diagnostic and therapeutic modalities, the survival of cancer patients after the definitive treatment is increasing^[2]. Nevertheless, they are at higher risk of developing a second primary malignancy. Studies have estimated that the incidence of two synchronous primary cancers was between 0.73% and 11.7% while the incidence of triple malignancy at 2 or 3 time points was up to 1.1%^[3]. Nonetheless, the incidence of synchronous triple malignancy is unknown and rare. According to Moertel^[4], synchronous primary cancer is defined as more than one primary cancer detected in a single patient within 6 months of diagnosis of the first malignancy while metachronous cancer is defined as second primary cancer beyond 6 months of diagnosis

of primary malignancy. According to Warren and Gates^[5], second primary cancer is defined as those second primary tumors with histopathological confirmed diagnosis, each must be geographically separated by normal mucosa and it should not arise from the metastasis of the first malignancy. The incidence of quadruple malignancy is found to be <0.1%^[6]. Multiple primary cancers need to be treated as a distinct entity in view of various permutation and combination related to the sequence and management of different cancers. Thus, management of quadruple malignancy case is a challenge to tackle. Therefore, in this case report and review of the literature, we discuss the dilemmas in diagnosis of three synchronous cancers along with the problems associated with deciding the treatment and sequence of management of all three simultaneous malignancies. We report a unique case of quadruple malignancy with history of sigmoid colon cancer as well as currently presented with squamous cell carcinoma (SCC) scalp, adenocarcinoma of prostate, and ascending colon cancer.

2. Case presentation

2.1. Scalp lesion

We present a case of 54-year-old gentleman, non-smoker with complaints of non-healing, pigmented ulcer in the right fronto-parietal area. He had history of sigmoid colon cancer for which he underwent segmental sigmoid colectomy and received FOLFOX (folinic acid, fluorouracil, and oxaliplatin) chemotherapy in 2011. Patient was disease free since then. He had a family history of colon cancer (first degree relative). He noted a rapidly progressing lesion on the forehead in the last 2 months. On examination, the lesion was 2 × 1 cm, two centimeter above the right eyebrow. There was no palpable node in the parotid area/right posterior neck/level 5. Histopathological report was consistent with SCC. Ultrasonography (USG) of the right parotid gland reveals one intraparotid node measuring 1 cm. USG-guided fine-needle aspiration cytology (FNAC) was done for the intraparotid node, which was suggestive of non-metastatic etiology. Positron emission tomography and computed tomography (PET CT) show metabolically active nodule in the right frontoparietal scalp. Therefore, he was planned for wide excision of the scalp lesion with primary closure of the defect.

2.2 Colon lesion

Patient underwent PET CT since he had a history of carcinoma sigmoid colon. PET CT reveals a metabolically active polypoidal lesion in the ascending colon with standardized uptake values (SUV) of 18.0. PET/CT scans demonstrated differential uptake of fluorodeoxyglucose (FDG) in enlarged preaortic, paraortic, inter aortocaval, retrocaval, retrocaval, bilateral common iliac, and right external iliac nodes (SUV max 3.9). Physical examination showed no tenderness/any mass in the abdomen. There were no hemorrhoids or fissures during rectal examination.

Patient did not show any significant weight loss. Laboratory investigation revealed normal hemoglobin values of 13.1 mg/dl. Endoscopic examination of the colon reveals ulceroproliferative lesion in the ascending colon (**Figure 1**). Histopathological report suggests dysplastic glands with villous configuration compatible with villous adenoma. The patient was preliminarily planned as unresectable since he had multiple mediastinal nodes.

2.3. Prostate cancer

PET CT also showed FDG avid area with no obvious CT evident lesion noted in peripheral mid zone of prostate gland (SUV max 6). Therefore, prostate specific antigen (PSA) test was done, where the level of PSA was found to be high (133 ng/mL). Hence, prostate specific membrane antigen (PSMA) PET was performed, suggestive of PSMA expressed lesion involving enlarged prostate, pelvic, retroperitoneal, right retrocaval, and mediastinal lymph nodes. Hence, he underwent trans rectal ultrasound guided biopsy (TRUS) of prostate. (**Figures 2 and 3**). His histopathological report suggested adenocarcinoma prostate with Gleason score of 5 + 5 = 10. Hence, patient was diagnosed as metastatic advanced prostate adenocarcinoma which did not render any surgical intervention.

3. Diagnostic dilemma

We faced a diagnostic dilemma for ulceroproliferative colon disease, as it was negative for malignancy on biopsy

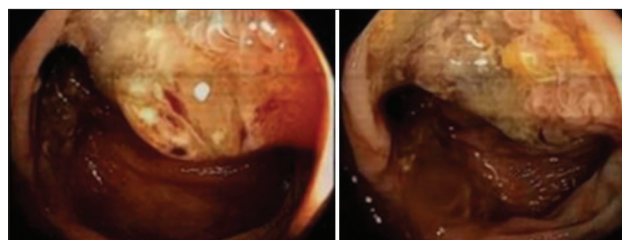


Figure 1. Colonoscopic findings of ulceroproliferative lesion in the ascending colon.

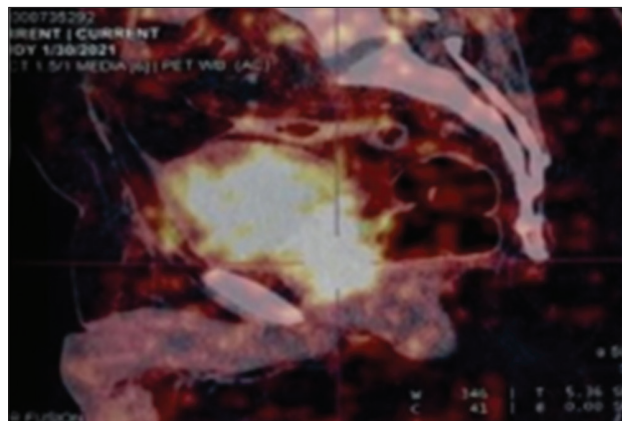


Figure 2. Prostate specific membrane antigen uptake is seen in entire enlarged prostate.

but PET scan showed lesion in the colon with multiple mediastinal nodes along with mild SUV uptake in prostate without any definitive lesion. Digital rectal examination revealed enlarged prostate, with an elevated PSA. Further, PSMA PET scan revealed PSA expressed lesions involving enlarged prostate and all the nodes mentioned previously having uptake on general PET scan. Hence, patient who was thought to have unresectable colon disease was transformed to resectable colon disease with metastatic prostate cancer who presented initially with a scalp lesion.

4. Treatment dilemma

Treatment options for scalp lesion with a history of excisional biopsy with positive margins include active surveillance (wait and watch), wide excision of scalp, or wide excision with superficial parotidectomy. For colon disease, treatment options include endoscopic removal of polypoidal growth or hemicolectomy of biopsy negative lesion. For prostate, surgical intervention was not recommended and advanced hormonal therapy/chemotherapy was the treatment option. Thus, there were 12 treatment alternatives available (**Table 1**) for a single patient which putting us in a difficult situation.

5. Sequential dilemma

Surgery was the definitive treatment option for colon and scalp malignancy while chemotherapy remains the main line of treatment for prostate cancer. This lands us in a sequential dilemma since one had to be preceded by other. Based on the available literature, **Table 1** shows the possible treatment options for three cancers along with their reasons for exclusion and Figure 4 shows sequential dilemma in management of these cancers.

6. Discussion

A literature search till date revealed only 21 quadruple malignancies with breast cancer being the most common

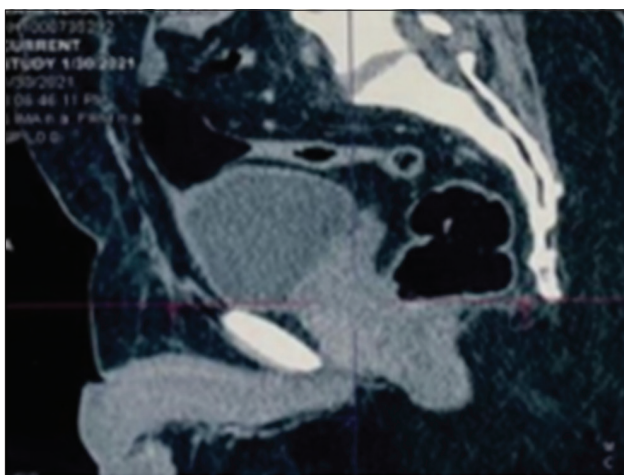


Figure 3. CT scan shows enlarged prostate with lesion infiltrating root of seminal vesicles and neck of urinary bladder.

synchronous malignancy. **Table 2** provides an update on quadruple malignancy in details^[7-26]. In this case report, we present a unique case with the combination of scalp, colon, and prostate cancers.

6.1. Scalp lesion

According to National Comprehensive Cancer Network (NCCN) guidelines^[27], wide excision with adequate margins of scalp lesion is standard of care in the management of scalp malignancy. However, in our case, the patient presented with history of excisional biopsy with positive margins. A study led by Huang and Boyce^[28] found that 50% of cutaneous SCC lesions with positive margins recurred with consequence increased risk of developing metastases. Intraparotid node is the first echelon nodes for scalp SCC. Advanced scalp SCC has 5% chances of intraparotid metastasis; therefore, superficial parotidectomy is recommended in high risk or recurrent scalp disease. This carries a risk of facial nerve paralysis ranging from 10% to 68%^[29]. Therefore, elective treatment of intraparotid lymph node in early scalp lesion is debatable. According to a meta-analysis conducted by de Bondt *et al.*^[30], USG-guided FNAC is sensitive and specific enough to accurately detect nodal metastasis; therefore, USG-guided FNAC was done for an enlarged node, and FNAC was reported to be negative for nodal metastasis. Hence, decision was taken for wide local excision of scalp lesion without superficial parotidectomy.

6.2. Colonic lesion

This patient presented with multiple mediastinal nodes with colonic lesion. Studies have rarely shown that mediastinal lymph node metastasis in advanced colon carcinoma without any other organ involvement. However, PSMA PET CT scan revealed the uptake of mediastinal node, shifting the diagnosis toward mediastinal metastasis from adenocarcinoma prostate. Studies have shown high cumulative risk of malignant transformation (up to 24%)^[31] of large polyp (> 1 cm). Considering previous history of sigmoid colon carcinoma and high volume disease that was not amenable to endoscopic excision, decision was taken to perform right hemicolectomy.

6.3. Prostate lesion

Advanced metastatic prostate cancers (AMPC) are not responsive to surgical/radiotherapy management.

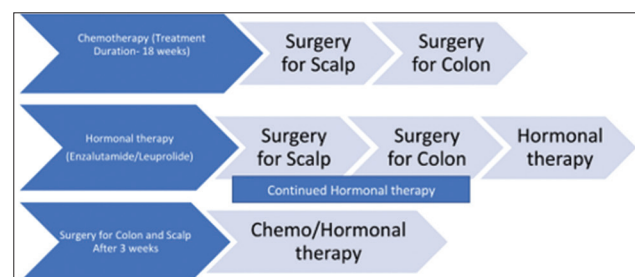


Figure 4. Sequential dilemma in management.

Table 1. Possible treatment options of triple malignancy case

Scalp lesion	Colonic lesion	Prostate lesion	Decision	Reason
WLE	Operate	Hormonal	Included	—
WLE	Observe	Hormonal	Excluded	A
WLE	Operate	Chemo + Hormonal	Excluded	B
WLE + SP	Operate	Hormonal	Excluded	C
Observe	Operate	Hormonal	Excluded	D
WLE	Observe	Chemo + Hormonal	Excluded	A and B
WLE + SP	Observe	Hormonal	Excluded	A and C
WLE + SP	Operate	Chemo + Hormonal	Excluded	B and C
Observe	Operate	Chemo + Hormonal	Excluded	B and D
Observe	Observe	Hormonal	Excluded	A and D
Observe	Observe	Chemo + Hormonal	Excluded	A, B and D
WLE + SP	Observe	Chemo + Hormonal	Excluded	A, B and C

A-Due to highly suspicious of colon polyp to be malignant; B-Chemotherapy will delay the surgical management; C-Parotid node reactive; D-Excisional biopsy with positive margins. Abbreviation: Chemo-chemotherapy. SP, superficial parotidectomy, WLE, wide local excision

Table 2. Literature review on quadruple malignancy from 1979 to 2020

Author	Age	Country	Year	Site of presentation	Other Site	Time points	Line of treatment
Clements and Gray ^[7]	64	USA	1979	Left kidney CA	<ul style="list-style-type: none"> • Right ureter (papillary carcinoma) • Right kidney upper pole (adeno CA) • Right renal pelvic (papillary carcinoma on a narrow pedicle) 	Synchronous	Surgery + Palliative
Abe <i>et al.</i> ^[8]	45	Japan	1991	Stomach (adeno CA)	<ul style="list-style-type: none"> • Colon (adeno CA) • Right ureteral cancer • Rectum (Borrmann II type CA) 	Three time points	Surgery + CT
Mori <i>et al.</i> ^[9]	64	Japan	1994	Bladder cancer	<ul style="list-style-type: none"> • Skin (BCC) • HCC anti HCV and anti HTLV +) • Vocal cord (SCC) 	Three time point	Curative (Surgery) + RT + CT
Murata <i>et al.</i> ^[10]	71	Japan	1994	Bowen's disease at chest	<ul style="list-style-type: none"> • Colon (adeno CA sigmoid) • Stomach (adeno CA) • Vocal cord (SCC) 	Two time points	Surgery + RT
Nakayama <i>et al.</i> ^[6]	62	Japan	1997	Right CA Breast (Solid tubular)	<ul style="list-style-type: none"> • Left CA Breast - Papillotubular vaters papilla (papillary adenocarcinoma) • Urinary bladder (transitional cell cancer) 	Four time points	Surgery + CT + HT

(Contd...)

Table 2. (Continued)

Author	Age	Country	Year	Site of presentation	Other Site	Time points	Line of treatment
Mitsubishi <i>et al.</i> ^[11]	67	Japan	2004	Urinary Bladder	<ul style="list-style-type: none"> • Oral cavity • Stomach • Lung 	Three time points	Curative (surgery)
Noh <i>et al.</i> ^[12]	68	Korea	2008	Breast	<ul style="list-style-type: none"> • Rectum (adeno CA) • CA ovary (adenocarcinoma) • Endometrium intraepithelial CA 	Metachronous	Surgery + CT
Atasever <i>et al.</i> ^[13]	50	Turkey	2009	NA	<ul style="list-style-type: none"> • Left ovary (papillary serous CA) • Left and right uterine tubes (micro invasive CA) • Endometrium (intraepithelial CA endometrium) • Uterine cervix (endocervical carcinoma) 	Synchronous	Surgery + CT
Angurana <i>et al.</i> ^[14]	35	India	2010	Right breast (Infiltrating ductal CA)	<ul style="list-style-type: none"> • Left Breast • Endometrial CA • Esophagus (SCC) 	Four time points	Curative (Surgery)
Yhim <i>et al.</i> ^[15]	60	Korea	2010	Liver (HCC)	<ul style="list-style-type: none"> • Bladder (papillary urothelial carcinoma) • Lung (SCC) • Stomach (Adeno) 	Two time points	Radiofrequency ablation + CT
Demirci <i>et al.</i> ^[16]	78	Turkey	2010	Right Breast	<ul style="list-style-type: none"> • CA ovary • Left Breast (IDC) • Renal hilus (NET) 	Four time points	Surgery + CT + RT
Kousaka <i>et al.</i> ^[17]	41	Japan	2011	Left lower leg (Osteosarcoma)	<ul style="list-style-type: none"> • Tongue • Thyroid • Right Breast 	Four time points	CT + Curative (Surgery)
Jiao <i>et al.</i> ^[18]	64	China	2013	Small intestine adenocarcinoma	<ul style="list-style-type: none"> • Descending colon (mucinous adeno CA) • Left renal CA • Pancreatic CA 	Four time points	Curative
Kim <i>et al.</i> ^[19]	73	Korea	2013	Papillary cancer thyroid	<ul style="list-style-type: none"> • Invasive ductal adenocarcinoma -- Breast adenocarcinoma • Pancreas • GIST 	Synchronous	HT and CT Palliative care
Milosevic <i>et al.</i> ^[20]	40	Serbia	2014	Medullary thyroid CA + two micropapillary thyroid CA	<ul style="list-style-type: none"> • Right scapula (melanoma) • Lobular melanoma • Breast carcinoma (lobular carcinoma <i>in situ</i>) 	Metachronous	Curative (surgery)+ RT + CT

(Contd...)

Table 2. (Continued)

Author	Age	Country	Year	Site of presentation	Other Site	Time points	Line of treatment
Maruyama <i>et al.</i> ^[21]	69	Japan	2015	Tongue SCC	<ul style="list-style-type: none"> • Right Breast invasive ductal • Left Breast invasive ductal • RCC 	Synchronous	Curative RT + HT
Elec <i>et al.</i> ^[22]	78	Romania	2017	Prostate adenocarcinoma	<ul style="list-style-type: none"> • c- Clear cell renal ccarcinoma • Papillary renal ccarcinoma • Small cell bladder cancer 	Synchronous	Curative (Surgery)
Nanashima <i>et al.</i> ^[23]	67	Japan	2017	Stomach	<ul style="list-style-type: none"> • Sigmoid colon • Rectum • Pancreas 	Synchronous	Curative (Surgery)+ CT
Wang and Yang ^[24]	56	China	2019	Cervix	<ul style="list-style-type: none"> • Endometrium • Ovary • Stomach 	Synchronous	Neoadjuvant CT + Curative (Surgery)
Albertsdottir and Juel ^[25]	70	Denmark	2020	Cervix (Adeno CA)	<ul style="list-style-type: none"> • Left thigh, Right elbow, • Right knee (BCC) • Right lower leg (Melanoma) • Breast (IDC) 	Synchronous	Curative + CT + HT (Surgery)
Maruyama <i>et al.</i> ^[26]	86	Japan	2020	Colon adenocarcinoma	<ul style="list-style-type: none"> • Foot (Angiosarcoma) • Oral (SCC) • Gastric Cancer 	Four time points	Neoadjuvant CT + Curative (Surgery)

BCC, basal cell carcinoma; CA, carcinoma; CT, chemotherapy; IDC, infiltrating ductal carcinoma; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HT, hormonal therapy; HTLV, human T lymphotropic virus; NET, neuroendocrine tumor; RCC, renal cell carcinoma; RT, radiotherapy; SCC, squamous cell carcinoma

According to the GETUG-AFU-15 and CHAARTED trials, androgen deprivation therapy (ADT) along with chemotherapy has been the standard of care for high volume AMPC^[32]. High volume disease includes the presence of visceral metastasis, a bone-metastasis beyond the axial skeleton. In our case, there was triple synchronous cancers including scalp and colon which needed immediate surgical management, combination of chemotherapy and ADT would entail delay in the management of scalp and colonic cancers by a period of 21 weeks. This could have resulted in flaring up of early curable colon cancer. ADT with advanced hormonal therapy is the alternative treatment for metastatic advanced prostate cancer^[33]. Therefore, decision was taken to give ADT along with newer antiandrogens like enzalutamide, which is an androgen-receptor signaling inhibitor. Enzalutamide has been known to improve overall survival in metastatic advanced prostate cancers^[34,35]. Hormonal therapy involved injection of leuprolide 22.5 mg once every 3 month and enzalutamide 160 mg once a day. Thus,

a distinct treatment modality was planned for the patient, considering the adverse and adjuvant effects of each modality, deciding between conservative or operative treatment, and sequences them accordingly.

7. Real-world scenarios

Patient underwent wide excision of scalp and laparoscopic assisted right hemicolectomy with ileocolic anastomosis preceded by advanced hormonal therapy. Post-operative pathological examination of colonic lesion confirmed moderately differentiated adenocarcinoma infiltrating up to submucosa without nodal metastasis. Pathological staging of the colonic tumor was pT1N0M0. Patient was not subjected to radiotherapy or chemotherapy as per NCCN guidelines. Post-operative pathological examination of scalp lesion confirmed residual moderately differentiated SCC. Pathological staging of scalp tumor was pT1N0M0 which did not warrant adjuvant therapy. Patient was continued on advanced hormonal therapy after surgery

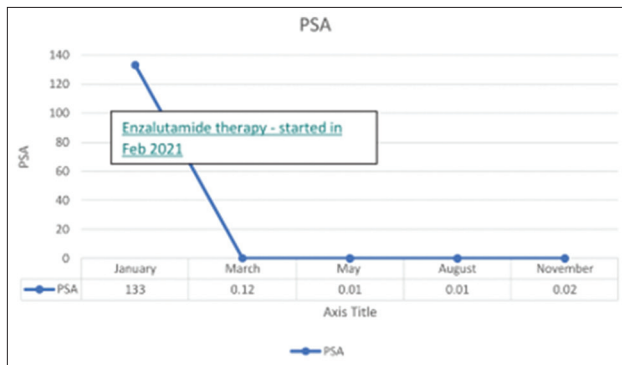


Figure 5. Decrease in prostate specific antigen levels after starting advanced hormonal therapy.

and discharged on post-operative day 7. He was on regular 3 monthly follow-up with PSA monitoring. Patient showed positive response to advanced hormonal therapy, indicated by decrease in PSA levels, from 133 ng/mL in pre-operative period to 0.02 ng/mL after 1 year (**Figure 5**) Patient was disease-free in last follow-up for scalp and colon cancers while progression free for prostate cancer.

8. Limitations

The patient was not subjected to genetic testing or counseling since he was not willing to do so. Genetic data could have been of great value to the patient and for the completion of the study. In the review of literature, we were unable to add case reports written in languages other than English.

9. Conclusion

Quadruple malignancies are rare entity. Investigation, interaction, sequence, and treatment options of individual cancers need to be taken into consideration while treating such synchronous malignancies. Multidisciplinary approach is the key toward its early diagnosis and optimal sequential treatment. Such patients are at significant risk of developing new cancer and recurrence, therefore strict adherence to follow-up protocols is necessary. Customized molecular and genetic testing play an important role in developing preventive strategies for early detection of multiple synchronous cancers.

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Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethics approval and consent to participate

Consent was taken from the patient to participate in this study.

Consent for publication

Consent was taken from the patient for publication.

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