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
adenocarcinoma 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, paraaortic, inter aortocaval,
retrocaval, retrocrural, 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 retrocrural, 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 synchronous malignancy. Table 2 provides an update on quadruple malignancy in details. 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, 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 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%. Therefore, elective treatment of intraparotid lymph node in early scalp lesion is debatable. According to a meta-analysis conducted by de Bondt et al., 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%) of large poly (> 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.
### Table 1. Possible treatment options of triple malignancy case

<table>
<thead>
<tr>
<th>Scalp lesion</th>
<th>Colonic lesion</th>
<th>Prostate lesion</th>
<th>Decision</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLE</td>
<td>Operate</td>
<td>Hormonal</td>
<td>Included</td>
<td>—</td>
</tr>
<tr>
<td>WLE</td>
<td>Observe</td>
<td>Hormonal</td>
<td>Excluded</td>
<td>A</td>
</tr>
<tr>
<td>WLE</td>
<td>Operate</td>
<td>Chemo + Hormonal</td>
<td>Excluded</td>
<td>B</td>
</tr>
<tr>
<td>WLE + SP</td>
<td>Operate</td>
<td>Hormonal</td>
<td>Excluded</td>
<td>C</td>
</tr>
<tr>
<td>Observe</td>
<td>Operate</td>
<td>Hormonal</td>
<td>Excluded</td>
<td>D</td>
</tr>
<tr>
<td>WLE</td>
<td>Observe</td>
<td>Chemo + Hormonal</td>
<td>Excluded</td>
<td>A and B</td>
</tr>
<tr>
<td>WLE + SP</td>
<td>Observe</td>
<td>Hormonal</td>
<td>Excluded</td>
<td>A and C</td>
</tr>
<tr>
<td>WLE + SP</td>
<td>Operate</td>
<td>Chemo + Hormonal</td>
<td>Excluded</td>
<td>B and C</td>
</tr>
<tr>
<td>Observe</td>
<td>Operate</td>
<td>Chemo + Hormonal</td>
<td>Excluded</td>
<td>B and D</td>
</tr>
<tr>
<td>Observe</td>
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<td>Hormonal</td>
<td>Excluded</td>
<td>A and D</td>
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<td>Chemo + Hormonal</td>
<td>Excluded</td>
<td>A, B and D</td>
</tr>
<tr>
<td>WLE + SP</td>
<td>Observe</td>
<td>Chemo + Hormonal</td>
<td>Excluded</td>
<td>A, B and C</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Country</th>
<th>Year</th>
<th>Site of presentation</th>
<th>Other Site</th>
<th>Time points</th>
<th>Line of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clements and Gray[7]</td>
<td>64</td>
<td>USA</td>
<td>1979</td>
<td>Left kidney CA</td>
<td>Right ureter (papillary carcinoma)</td>
<td>Synchronous</td>
<td>Surgery + Palliative</td>
</tr>
<tr>
<td>Abe et al.[8]</td>
<td>45</td>
<td>Japan</td>
<td>1991</td>
<td>Stomach (adenoc CA)</td>
<td>Colon (adenoc CA)</td>
<td>Three time points</td>
<td>Surgery + CT</td>
</tr>
<tr>
<td>Mori et al.[9]</td>
<td>64</td>
<td>Japan</td>
<td>1994</td>
<td>Bladder cancer</td>
<td>Skin (BCC)</td>
<td>Three time points</td>
<td>Curative (Surgery) + RT + CT</td>
</tr>
<tr>
<td>Murata et al.[10]</td>
<td>71</td>
<td>Japan</td>
<td>1994</td>
<td>Bowen’s disease at chest</td>
<td>Colon (adenoc CA sigmoid)</td>
<td>Two time points</td>
<td>Surgery + RT</td>
</tr>
<tr>
<td>Nakayama et al.[6]</td>
<td>62</td>
<td>Japan</td>
<td>1997</td>
<td>Right CA Breast (Solid tubular)</td>
<td>Left CA Breast - Papillotubular vaters papilla (papillary adenocarinoma)</td>
<td>Four time points</td>
<td>Surgery + CT + HT</td>
</tr>
</tbody>
</table>

(Contd...)
<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Country</th>
<th>Year</th>
<th>Site of presentation</th>
<th>Other Site</th>
<th>Time points</th>
<th>Line of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitsuhashi et al.</td>
<td>67</td>
<td>Japan</td>
<td>2004</td>
<td>Urinary Bladder</td>
<td>• Oral cavity • Stomach • Lung</td>
<td>Three time points</td>
<td>Curative (surgery)</td>
</tr>
<tr>
<td>Noh et al.</td>
<td>68</td>
<td>Korea</td>
<td>2008</td>
<td>Breast</td>
<td>• Rectum (adeno CA) • CA ovary (adenocarcinoma) • Endometrium intraepithelial CA</td>
<td>Metachronous</td>
<td>Surgery + CT</td>
</tr>
<tr>
<td>Atasever et al.</td>
<td>50</td>
<td>Turkey</td>
<td>2009</td>
<td>NA</td>
<td>• Left ovary (papillary serous CA) • Left and right uterine tubes (micro invasive CA) • Endometrium (intraepithelial CA endometrium) • Uterine cervix (endocervical carcinoma)</td>
<td>Synchronous</td>
<td>Surgery + CT</td>
</tr>
<tr>
<td>Angurana et al.</td>
<td>35</td>
<td>India</td>
<td>2010</td>
<td>Right breast (Infiltrating ductal CA)</td>
<td>• Left Breast • Endometrial CA • Esophagus (SCC)</td>
<td>Four time points</td>
<td>Curative (Surgery)</td>
</tr>
<tr>
<td>Yhim et al.</td>
<td>60</td>
<td>Korea</td>
<td>2010</td>
<td>Liver (HCC)</td>
<td>• Bladder (papillary urothelial carcinoma) • Lung (SCC) • Stomach (Adeno)</td>
<td>Two time points</td>
<td>Radiofreqency ablation + CT</td>
</tr>
<tr>
<td>Demirci et al.</td>
<td>78</td>
<td>Turkey</td>
<td>2010</td>
<td>Right Breast</td>
<td>• CA ovary • Left Breast (IDC) • Renal hilus (NET)</td>
<td>Four time points</td>
<td>Surgery + CT + RT</td>
</tr>
<tr>
<td>Kousaka et al.</td>
<td>41</td>
<td>Japan</td>
<td>2011</td>
<td>Left lower leg (Osteosarcoma)</td>
<td>• Tongue • Thyroid • Right Breast</td>
<td>Four time points</td>
<td>CT + Curative (Surgery)</td>
</tr>
<tr>
<td>Jiao et al.</td>
<td>64</td>
<td>China</td>
<td>2013</td>
<td>Small intestine adenocarcinoma</td>
<td>• Descending colon (mucinous adenocarcinoma) • Left renal CA • Pancreatic CA</td>
<td>Four time points</td>
<td>Curative</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>73</td>
<td>Korea</td>
<td>2013</td>
<td>Papillary cancer thyroid</td>
<td>• Invasive ductal adenocarcinoma -- Breast adenocarcinoma • Pancreas • GIST</td>
<td>Synchronous</td>
<td>HT and CT Palliative care</td>
</tr>
<tr>
<td>Milosevic et al.</td>
<td>40</td>
<td>Serbia</td>
<td>2014</td>
<td>Medullary thyroid CA + two micropapillary thyroid CA</td>
<td>• Right scapula (melanoma) • Lobular melanoma • Breast carcinoma (lobular carcinoma in situ)</td>
<td>Metachronous</td>
<td>Curative (surgery)+ RT + CT</td>
</tr>
</tbody>
</table>

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


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DOI: 10.1186/1757-1626-3-53


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