Case Report

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Li-Fraumeni syndrome in the setting of re-occurring malignancies after 27 years of remission: a case report

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Introduction and importance: Multiple primary tumors are defined as multiple simultaneous (within 6 months) or heterogeneous tumors.

Case presentation: Here, the authors present the case of a 58-year-old Saudi female patient with Li-Fraumeni syndrome who has multiple primary tumors.

Clinical discussion: The surgical cytoreduction or 'debulking' technique is the main treatment option started in individuals with High Grade Serous Ovarian CanceR. This surgical strategy aims to completely remove all disseminated tumor masses that are present in the patient's peritoneal cavity on a macroscopic level.

Conclusion: In conclusion, in our case, she has developed her ovarian cancer 27 years after her breast cancer got treated. This was already stage IIIB to stage IV. If it was not for her incidental discovery of her urinary bladder cancer, which is most likely is a long-term sequel of using cyclophosphamide 27 years ago. Multiple primary tumors are defined as multiple simultaneous (within 6 months) or heterogeneous tumors. Here, the authors present the case of a 58-year-old Saudi female patient with Li-Fraumeni syndrome who has multiple primary tumors. In conclusion, in our case, she has developed her ovarian cancer 27 years after her breast cancer got treated. This was already stage IIIB to stage IV. If it was not for her incidental discovery of her urinary bladder cancer, which is most likely is a long-term sequel of using cyclophosphamide 27 years ago.

Keywords: cancer, Li-Fraumeni syndrome, malignancies, oncology

Introduction

Multiple primary tumors are defined as multiple simultaneous (within 6 months) or heterogeneous tumors to the same patient. The exact definition of multiple primary tumors varies from one study to another. It is identified when the tumor occurs in a different location and/or has a different histology[1].

Patients with multiple primary tumors must be thoroughly investigated to establish the occurrence of a hereditary tumors. This information can be useful to physicians to assess cancer risk and optimize treatment[2].

HIGHLIGHTS

- In our case, she has developed her ovarian cancer 27 years after her breast cancer got treated.
- Genetic counseling and predictive testing should be offered to patients and families meeting criteria such as classic Li-Fraumeni syndrome or Li-Fraumeni to encourage improved cancer screening if Li-Fraumeni syndrome is confirmed.
- If this patient had an immediate total colectomy after the discovery of stage I colon cancer may she would be cured from her colon cancer and she would be now free of all the three cancers.
- The big question in this case is: why did her body stayed in re-emission for 27 years?

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant cancer susceptibility syndrome caused by mutations in the germline gene TP53 and it is the only known pathogenic genes for LFS. It is characterized by a high risk of developing early cancer and has been clinically confirmed to be associated with multiple primary tumors[3,4].

The tumors most commonly associated with LFS are breast cancer, soft tissue sarcoma, osteosarcoma, brain cancer, adrenocortical carcinoma, and leukemia[5].

Early detection of this mutation can effectively help doctors manage treatment and achieve the best possible treatment. In such cases, monitoring and active prophylactic treatment can provide positive results for patients with this mutation and their relatives[1].

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Genetic counseling and predictive testing should be offered to patients and families meeting criteria such as classic LFS or Li-Fraumeni to encourage improved cancer screening if LFS is confirmed. Although the NCCN (The National Comprehensive Cancer Network) guidelines recommend testing individual cases with the LFS marker even without a family history, others reject the need for testing because of the low mutation rate (0–7%) and high psychological burden[6].

In the future, screening of early-stage breast cancer patients without a family history of cancer will become more feasible as screening costs decrease and effective prevention strategies are validated[6]. Compared with other neoplastic syndromes such as hereditary breast and ovarian cancer, prophylactic surgery does not provide a good prognosis for TP53 mutation carriers and each case must be considered individually[6].

Here, we present the case of a 58-year-old Saudi female patient with LFS who has multiple primary tumors. This work was done by following the Surgical CAse REport (SCARE) criteria[7].

Case presentation

A 58-year-old Saudi woman with a history of breast cancer who was treated with chemotherapy and radiation in 1994. Her issue started back in March 2021 when she complained of lower abdomen pain, blood in urine, urine frequency, urgency, and incomplete bladder emptying. An ultrasound was done, showing highly suspicious ovarian masses and urinary bladder masses. A computerized tomography (CT) scan for the chest, abdomen, and pelvis was followed. The CT scan of the chest showed an unremarkable left mastectomy surgical bed with no enlarged axillary, supraclavicular lymph nodes, and mediastinal lymph nodes, and no findings to suggest lung metastatic disease. Abdomen and pelvis CT scans showed moderate to severe ascites with areas of omental thickening, bilateral adnexal masses suggestive of ovarian malignancy, and a small focal nodule in the urinary bladder (Fig. 1).

Our patient had a cystoscopy and trans urethral resection of bladder tumour done, and it has showed normal urethra, four bladder masses the largest below the right ureteric orifice in the trigon area, other two at the right posterior wall, and one at the middle posterior wall, bladder neck was free. Bladder carcinoma with no invasive component grade T1G3 was diagnosed (Fig. 2). Four weeks later, a repeat of her cystoscope was done and showed a recurring three masses, which mandates urgent start of therapy. The patient has received six doses of intravesical BCG over six weeks' time. The last dose was in the first week of June 2021. A revision cystoscope was done in October 2021 that showed a recurrence. This was either because the BCG was defected or the tumor was not responding and starting intravesical Gemcitabine was planned. As the tumor is not invading into the muscles we are going to discuss and need to make a brave scientific-based decision regarding adding immunotherapy to the gemcitabine.

At the same time, she was discovered to have a mass in the left adnexa with peritoneal and omental carcinomatosis. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy and peritoneal fluid sample in May 2021. The pathology showed serous carcinoma high grade, stage PT3ANX. The discussion at that time is to wait for eight weeks to finish BCG therapy then starting ovarian chemotherapy. The patient finished three cycles of her ovarian cancer chemo. Every cycle is followed by five doses of subcutaneous GMCSF 300 mcg and NIVESTIM 300 mcg.

A screening colonoscopy was done in August 2021 and showed normal colonic mucosa. A nonobstructing descending colon mass was seen at 35 cm, multiple biopsies were taken. Mild left sided diverticulosis was seen. Rectal retroflexion showed small hemorrhoids.

Biopsies showed moderately differentiated adenocarcinoma (Fig. 3).

At that time, the decision was made based on the fact that there is any obstructive symptoms from the colon or bleeding from the primary tumor in the colon, so in terms of the descending colon cancer, there is no immediate indication for an operation for the colon. The patient has stage IV ovarian cancer with carcinomatosis and ascites. The priority is the treatment for the ovarian cancer for that time.

Colectomy or diversion can be considered if there is any obstructive symptoms from the colon. Furthermore, colectomy can be considered if it was part of a cytoreductive procedure combined with gynecology, then at that time colectomy can be considered.

The following plan was agreed on by the team: The patient needs to start chemotherapy for ovarian cancer as a priority. Bladder cancer to be managed and endoscopically resected by urology between cycles of chemotherapy. Re-assess tumor markers during and after treatment. Re-evaluate with the Tumor Board with presence of gynecologic after the end of treatment to discuss if this patient would benefit from cytoreduction/Hyperthermic intraperitoneal chemotherapy. Colon cancer should only be considered for resection if the patient will undergo cytoreduction of all peritoneal and ovarian cancers. Otherwise, if she is deemed unresectable or not a candidate for surgical intervention upon completion of chemotherapy, we should be focusing only on palliative measures. The decision after discovering stage I colon cancer yet waiting till ovarian chemotherapy cycles are over was not the best decision as it was already too late for her colon cancer, which reached to stage IV. Four weeks after her last cycle of chemotherapy for her ovarian cancer she has developed ascites and CA 125 was high in the ascitic fluid. Colon surgeons said she has resistant ovarian cancer, and she was referred back to receive liposomal doxorubicin yet when opened surgically in a tertiary center in the United States it was found to be colon cancer Ascites and she did not need further therapy for her ovarian cancer.

Whole exome sequencing (sequencing including NGS-based CNV analysis) was done and showed a heterozygous pathogenic variant in the TP53 gene. This result is consistent with the genetic diagnosis of autosomal dominant LFS.

Now this patient has three active primary cancers and a history of a treated one. Her germline mutation is significant for the P53 mutation. We will get her sons and daughters to go for genetic testing.

Discussion

Host-related, the way of living, and environmental effects are all common etiological factors that may predispose individuals to multiple primary tumors. The relevant genetic examination and testing are described for some of the most frequent cancer risks

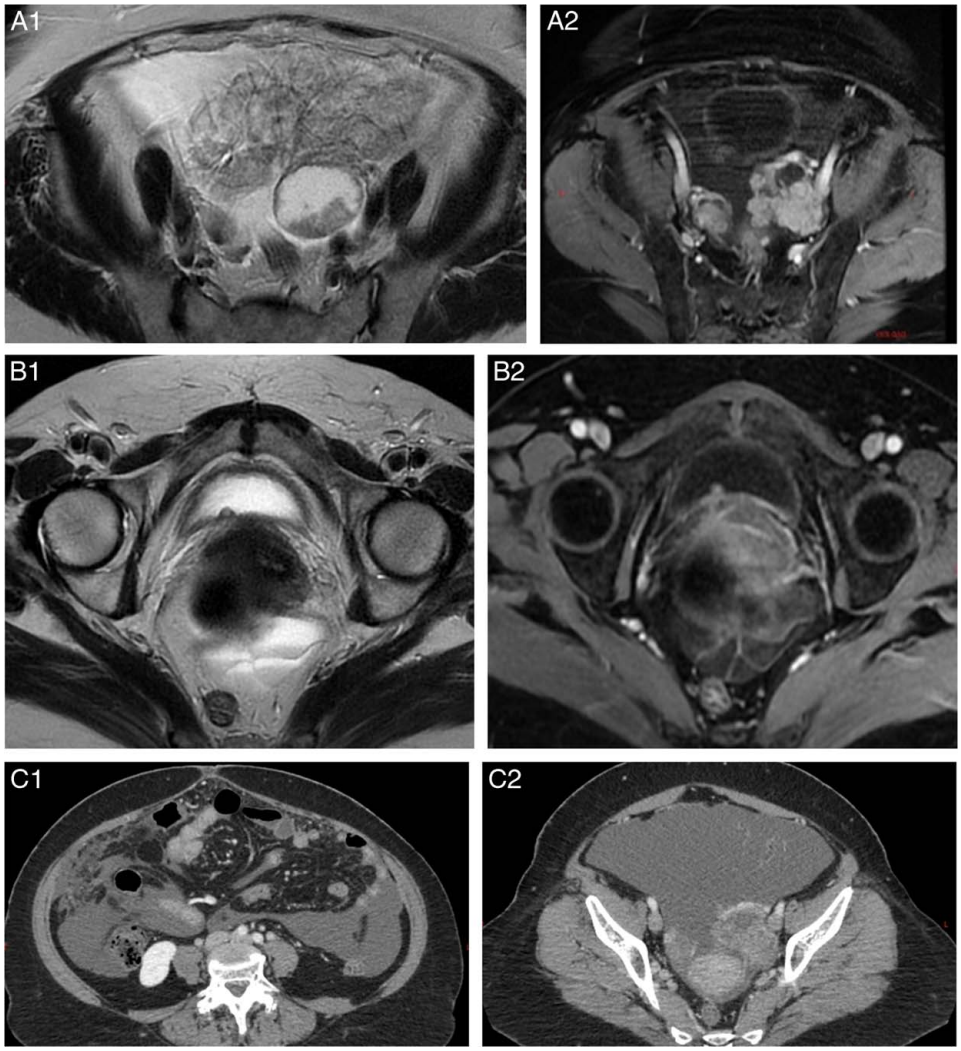

Figure 1. (A1) Axial T2 and (A2) Axial T1 post contrast images of the pelvis showing bilateral ovarian complex enhancing lesions in keeping with ovarian neoplasm with ascites. (B1) Axial T2 and (B2) Axial T1 post contrast images of the pelvis showing focal enhancing urinary bladder nodule and complex ascites with enhancing septations. (C1, C2) Contrast enhanced computed tomography images of the abdomen and pelvis showing ascites with omental thickening and peritoneal deposits.

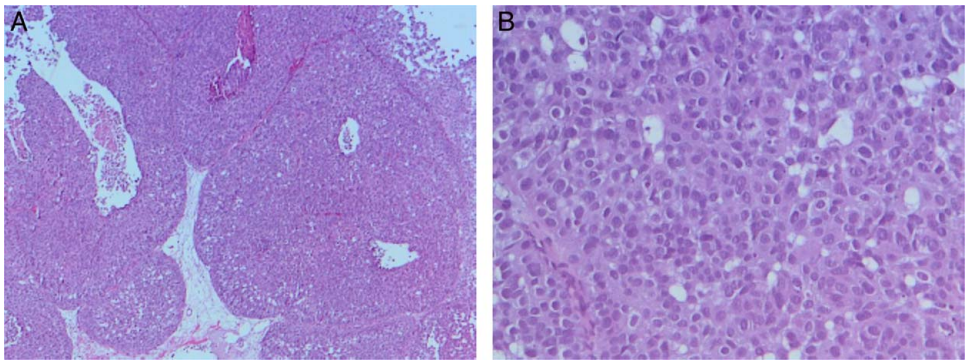

Figure 2. (A) low power view showing few fragments of urinary bladder mucosa, the deepest point of invasion of the tumor invading lamina propria, (B) high power view showing polymorphic cells with large nuclei, hyperchromatic nucleoli, scattered mitotic figures, and cells necrosis.

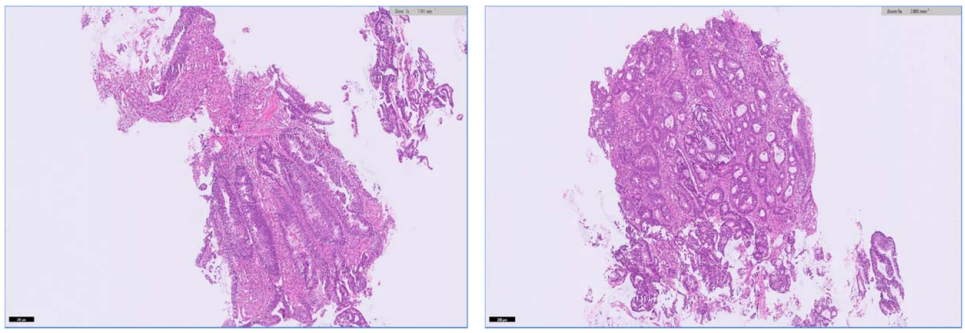

Figure 3. Microscopic examination shows lesioned tissue infiltrated by neoplastic cells arranged in glandular architecture lined by pleomorphic hyperchromatic nuclei with prominent nucleolus in a fibrotic background with desmoplastic reactions.

based on clinical presentation. Moreover, we discuss core principles and therapeutic options for patients with synchronous multiple primary tumors. Breast cancer risk is significantly increased by inherited mutations in the TP53 gene[8].

Up to 85% of breast cancer cases in women with germline TP53 gene mutations by the time they are 60 years old. The modes of treatment that has been used in our patient is chemotherapy, radiation, and cyclophosphamide where as it has been reported that in order to avoid or limit radiotherapy, mastectomy is preferred for the treatment of breast cancer. The likelihood of getting a second or third primary malignancy is significant, and the best form of surveillance is still unknown[9].

The TP53 mutation was discovered to be in 50% of bladder cancer patients. Currently, the main treatments for muscle-invasive bladder cancer include surgery and chemotherapy. Further studies has been taken into consideration when analyzing bladder cancer with the TP53 mutation, revealing molecular pathologic data obtained on the initial, nonmuscle invasive tumor, and the final cystectomy specimen, which showed the same TP53 mutation according to molecular pathology data. Regarding the treatment plan, three medications—mitomycin-C, doxorubicin, and gemcitabine, were especially more sensitive[10].

As for this patient, she received six doses of intravesical BCG over 6 weeks' time; in addition to, intravesical Gemcitabine with immunotherapy.

Approximately 96 percent of the High Grade Serous Ovarian Cancer (HGSOC) samples were discovered to have somatic TP53 mutations, which appears to indicate that this mutation is a defining characteristic of the disease and is probably necessary for its onset. Therefore, one could draw the conclusion that TP53 mutations are almost always present in HGSOC[11].

The surgical cytoreduction or 'debulking' technique is the main treatment option started in individuals with HGSOC. This surgical strategy aims to completely remove all disseminated tumor masses that are present in the patient's peritoneal cavity on a macroscopic level[12].

Due to the extensive distribution of the numerous metastatic foci, which frequently inhibits complete cytoreduction, advanced patients have a decreased chance of surgical success[13].

Almost all HGSOC patients who have successful cytoreductive surgery are advised to have adjuvant chemotherapy. Hence, our patient received three cycles of chemo and with each cycle followed by 5 doses of subcutaneous GMCSF 300 mcg NIVESTIM 300 mcg.

The majority of colorectal carcinomas develop following adenomatous polyps' malignant transformation. Tumor suppressor genes (P53) are inactivated during this transformation[14].

For localized, nonmetastatic stage colon cancer at any age, with an acceptable performance status and minimized comorbidities, surgical resection is the primary treatment option. Endoscopic resection is only used for certain early-stage, favorable-risk colon cancers. All colon cancer stage III and above patients should receive adjuvant therapy, as should each stage II patient with high risk characteristics. Nonsurgical candidates with unresectable locally advanced disease or a heavy burden of metastatic disease are offered palliative systemic chemotherapy to improve quality of life and lengthen survival[15].

After the last chemo dose an advised plan would be carried to perform a total colectomy for this patient. With this complex picture of having urinary bladder cancer and high grade ovarian cancer and colon cancer active in the same time, it is important to mention that we have given our instructions to encourage plant based food as much as possible and to avoid red meat and all processed meat and to increase fibers in the meals. We have encouraged going for intermittent fasting 2–3 days per week and we have started the patient on Metformin 1000 mg bid. These steps were given to arrange for reducing the continuous active risk of colon inflammation and to stimulate autophagy hoping this can help and support the action of the chemotherapy used to help this patient.

Conclusion

In conclusion, in our case, she has developed her ovarian cancer 27 years after her breast cancer got treated. This was already stage IIIB to stage IV. If it was not for her incidental discovery of her urinary bladder cancer that mosly is a long-term sequel of using cyclophosphamide 27 years ago. It is very odd that her urinary bladder cancer has started in the same time her ovarian and colon cancer got started. No real explanation for this synchronization in time. The big question in this case is why did her body stayed in re-emission for 27 years. We think that this could be related to when she underwent a bone marrow transplantation as a trial. This bone marrow transplantation could have been the reason that she was in full remission for 27 years.

Now in her second presentation there was crucial points that could have saved this patient from her current hustle. Waiting for

8 weeks to finish BCG therapy then starting ovarian chemotherapy that has worsen the case prognosis. This patient's stage I colon cancer was discovered while she was on chemotherapy for her stage IIIB ovarian cancer. Because of that, the surgeons thought it is better not to touch the colon for now and to concentrate on treating the advanced ovarian cancer very quickly. Because of this decision this patient now is in remission from her ovarian cancer but her stage I colon cancer has become stage IV with metastasis to the liver.

If this patient had an immediate total colectomy after the discovery of stage I colon cancer may she would be cured from her colon cancer and she would be now free of all the three cancers.

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