Endocervical Adenocarcinoma as a Secondary Malignancy in a Patient Treated for Non-Hodgkin's Lymphoma: A Case Report with Review of Literature

Garima Dhull[1] Minakshi Bhardwaj[1] Stuti Gupta[2] Mukta Pujani[1] Varsha Chauhan[1] Neha Garg[1] J.C Sharma[2] Sunita Malik[2]

[1] Department of Pathology, Employees State Insurance Corporation Medical College and Hospital, Faridabad, Haryana, India
[2] Department of Obstetrics & Gynecology, Employees State Insurance Corporation Medical College and Hospital, Faridabad, Haryana, India

Address for correspondence Mukta Pujani, MD, MAMS, Department of Pathology, Employees State Insurance Corporation Medical College and Hospital, NIT 3, Faridabad, Haryana 121012, India (e-mail: drmuktapujani@gmail.com).

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Abstract

Secondary malignancy can arise in patients with non-Hodgkin's lymphoma (NHL) on long follow-up. The risk of developing secondary malignancies is increased in NHL survivors, as compared to normal population and varies according to age, gender, and treatment modality. The nature of solid organ malignancy in order of frequency includes lung cancer followed by prostate, bladder, colon, breast, etc. Gynecological malignancy occurring in an NHL survivor is an extremely rare phenomenon with a low observed/expected ratio (0.89–0.93) as compared to other solid tumors. We hereby report a case of endocervical adenocarcinoma arising in a 51-year-old female patient who was a known treated case of NHL. This case highlights the fact that chemotherapy-induced atypia may mimic malignancy as well as the rare occurrence of gynecological cancers as a secondary malignancy in patients with NHL.

Keywords

- secondary malignancy
- NHL
- endocervical adenocarcinoma
- gynecological malignancy
- case report

Introduction

Successful treatment of Hodgkin's lymphoma has led to extensive study of secondary cancers and late sequelae of this malignancy. In contrast, relatively little information on secondary cancers is available for non-Hodgkin lymphomas (NHLs) because treatments for NHL have been less effective. Secondary malignancies (SMs) are of two types: synchronous (when second cancer is diagnosed within 6 months of the primary), and metachronous (SM is diagnosed after 6 months of diagnosing the primary). Patients with NHL are at increased risk of developing second malignancies; depending on the age of diagnosis, gender, and type of treatment taken for lymphoma.[1]

Case Report

A 51-year-old female patient, who had already completed her radiotherapy and chemotherapy for diffuse large B cell lymphoma and nasopharynx 2 years before, now presented in the gynecology outpatient department with complaints of vaginal discharge and pain in the abdomen since the last 3 months. Positron emission tomography-computed tomography scan was performed and revealed fludeoxyglucose avidity along the cervix and pyometra and an irregular polypoidal growth in the cervix.

Endometrial biopsy was performed. On performing histology, possibility of well- differentiated endometrial adenocarcinoma cannot be ruled out and in view of history of chemoradiotherapy for lymphoma, possibility of chemotherapy-induced atypia was suggested. Following endometrial biopsy, after 2 weeks endocervical curettage of the same patient was sent for histopathological examination. The examination was suggestive of endocervical polyp with a dense inflammatory infiltrate comprising of neutrophils, lymphocytes, plasma cells, and chemotherapy-induced atypia. Following this

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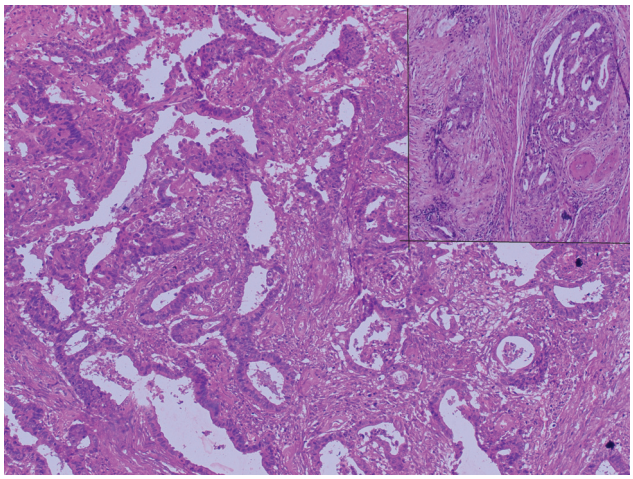

Fig. 1 Photomicrograph from cervix shows a tumor composed of cells arranged in glandular, tubular, and cribriform patterns (inset).

biopsy, a radical hysterectomy was performed almost 1 month later.

Histopathological sections taken from the cervix and isthmus showed a tumor composed of cells arranged in glandular, tubular, and cribriform patterns. Tumor cells were cuboidal-to-low columnar in shape with moderate amount of cytoplasm, round-to-oval moderately pleomorphic nuclei with coarse chromatin and brisk mitosis (►**Fig. 1**). Histopathological sections from body, fundus, bilateral tubes, ovaries, and parametrium were unremarkable. To ascertain the origin of the tumor, immunohistochemistry was performed, and the tumor was estrogen receptor, progesterone receptor, and vimentin negative; ruling out endometrial origin. Carcinoembryonic antigen was positive suggesting tumor to be of cervical origin (►**Fig. 2**). Final examination revealed well-differentiated endocervical adenocarcinoma.

Discussion

Metachronous second malignancy can occur in NHL survivors. The risk of developing second malignancies is increased in NHL survivors, as compared to normal population and varies according to age, gender, and treatment modality. A combination of clinical assessment, imaging, histopathology, as well as advanced techniques are required to ascertain if a new cancer in an NHL survivor is an SM. The key point is to differentiate a recurrence from a new unrelated cancer and guide appropriate management.

The latent period for developing SMs in NHL survivors is variable. However, usually such risk increases considerably after a particular period following diagnosis and treatment of the primary lymphoma and literature documents that the risk of developing second cancers, both hematologic as well as solid cancers, remains for decades after the initial malignancy diagnosis. The Berlin-Frankfurt-Muenster study group documented that the median latent period for the

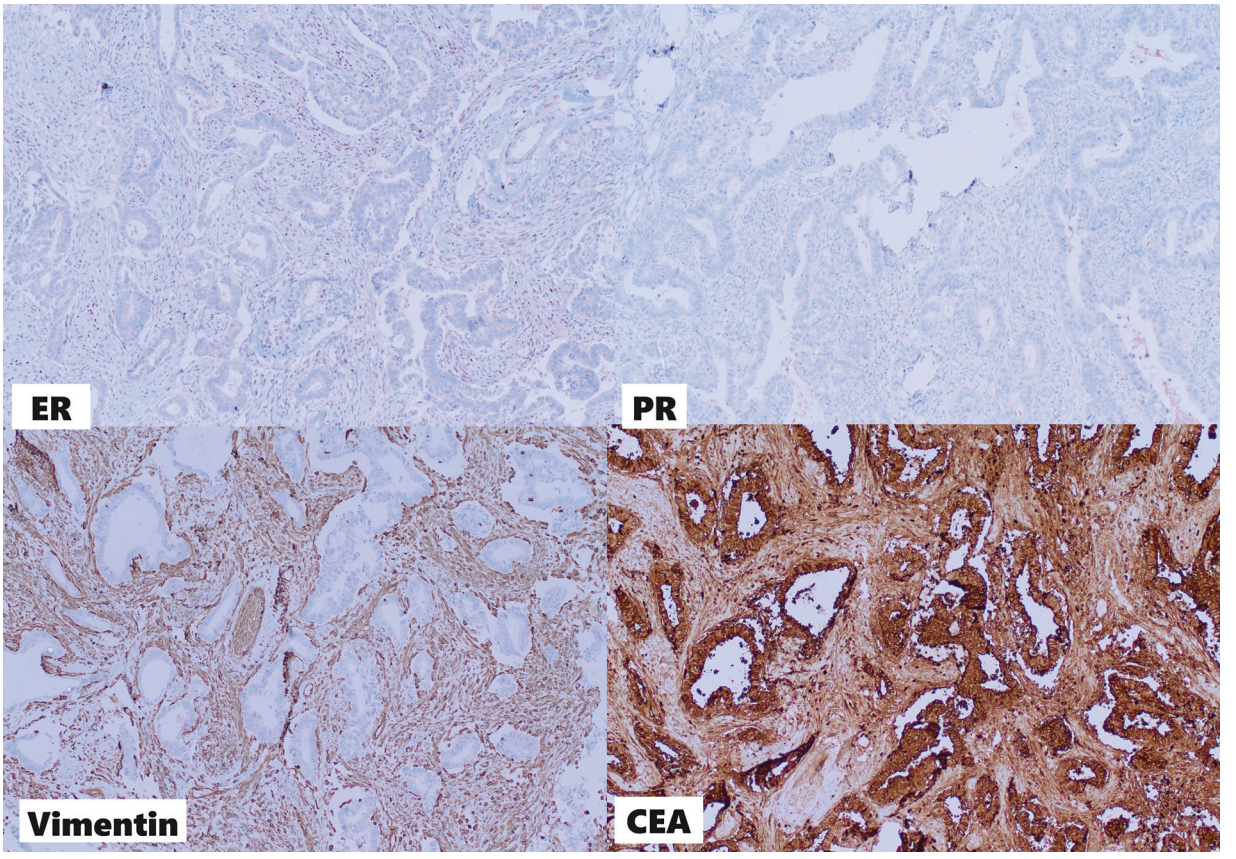

Fig. 2 Immunohistochemistry: estrogen receptor (ER), progesterone receptor (PR), and vimentin negative in tumor cells while carcinoembryonic antigen (CEA) positive.

development of secondary malignancy (SM) was 8.7 years with a wide range of 0.2 to 30.3 years. The median time to development of all carcinomas was 15.9 years (range, 0.7–30.3 years), while after excluding basal cell carcinomas it was 11.6 years (range, 0.7–23.7 years).[2] Parsons et al[1] conducted the largest study (142,637 patients with NHL) to examine second malignancy risk in patients with NHL with the longest follow-up period (40 years). They concluded that treatment with radiotherapy had the same overall risk of second malignancy as in untreated patients, while treatment with chemotherapy was seen to be associated with overall increased risk of developing second malignancies.[1] However, rituximab as a chemotherapeutic agent has substantially improved the outcome of patients with B-cell NHL. After treatment, patients with NHL experienced elevated risks for late toxicities, therapy-related leukemia, and several solid tumors.[3]

Tward et al studied SMs, which developed in 5,638 patients with NHL after treatment for 30 years. They found the rate to be significantly higher than the endemic rate (observed to expected ratio (O/E) 1:1.14, $p < 0.001$). Irradiated patients had a similar rate of malignancy compared to unirradiated patients. Gynecological malignancies were rarely observed with O/E ratio 0.96 and an excess risk in negative (−0.29).[4]

The increased risk of lung cancer associated with radiotherapy is well known. The other solid tumors commonly observed as second malignancy in order of frequency were prostate, bladder, colon, and breast. There has been evidence of second gynecological malignancies, but O/E ratio is less (0.89–0.93) as compared to other solid tumors.[1,4–7]

Pirani et al conducted a meta-analysis on 23 studies on the risk of SM in NHL survivors and concluded that there is a higher risk for SMs in patients with NHL compared to the general population with variable impact of different treatment modalities on relative risk.[6]

It is pertinent to mention that the limitations include a lack of definitive labeling as true SM from synchronous or metachronous cancers. Moreover, this being a single case report, further large-scale multicentric research is recommended to analyze such associations to enable preventive strategies like alterations in the treatment of NHL in terms of dosage/decreasing the number of cycles of chemoradiotherapy or devising follow-up strategies for patients at high risk for SM.

Conclusion

This case reemphasizes two points: first, chemoradiotherapy received by the patient for NHL may result in therapy-induced changes in the cells, which can mimic malignancy, hence, the pathologists need to be aware of both the possibilities and be extra cautious in making a definitive diagnosis on biopsies. Second, in an NHL survivor, SM may develop with a variable latency and may be hematological or solid organ cancer wherein lung/prostate/colon and breast being common. Gynecological malignancy occurring as an SM in an NHL survivor is unusual. This case highlights the need for screening and long-term follow-up in NHL survivors. Limitations include a lack of definitive labeling as true SM from synchronous or metachronous cancers as well as this a being single case report, further large-scale, multicentric research is warranted on the subject.

Patients' Consent

The authors confirm that all necessary patient consent forms have been obtained. The patient has provided written permission for their medical images and clinical details to be included in this publication. They have been informed that their identity will be protected by withholding their name and initials.

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Conflict of Interest

None declared.

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