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Case Report

An Unusual Coexistence of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma with Endometrioid-Type Endometrial Cancer in a 58-Year-Old Woman: A Case Study with Literature Review

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Keywords
Small lymphocytic lymphoma · Chronic lymphocytic leukemia · Endometrial adenocarcinoma · Hysterectomy

Abstract
Introduction: The coexistence of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with different gynecologic neoplasms is a rare phenomenon. Here, we report a case of simultaneously developed CLL/SLL with endometrioid-type uterine cancer. ***Case Report:*** A 58-year-old woman was admitted to the 2nd Department of Gynecology, Lublin Medical University, Lublin, Poland, in June 2017, where the uterine cancer was diagnosed. After the surgery, pathological examination revealed a uterine moderately differentiated adenocarcinoma of endometrioid subtype (subtype I according to Bokhman) deeply infiltrating the myometrium as well as the uterine cervix. Surprisingly, CLL/SLL was subsequently diagnosed in all removed pelvic as well as para-aortic lymph nodes. Immunohistochemical analysis showed CD45 (++),

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CD20 (+), CD3 (–/+), CD19 (+), CD23 (+), CD5 (+), and CD34 (+). Proliferative activity, assessed by MIB-1 proliferative index immunostaining, reached 18%. The patient was admitted to radiotherapy and chemotherapy at the Oncology Hospital, Lublin, Poland, and is still on follow-up. ***Conclusions:*** The coexistence of CLL/SLL with various gynecological malignancies, especially primary human endometrial cancer, is a rare entity. The detection of both tumors simultaneously, in general, is accidental, and the management should not be different from the situation in which malignancy appears de novo.

Introduction

Small lymphocytic lymphoma (SLL) is a non-Hodgkin lymphoma (NHL) which affects the B-cell lymphocytes of the immune system [1]. These B cells may be present in lymph nodes as well as in the lymphoid tissue, such as the spleen and the tonsils [1].

SLL has significant similarities to chronic lymphocytic leukemia (CLL) which also affects the B cells, primarily in the blood and bone marrow, with the possibility of lymph node involvement [1]. SLL and CLL are classified as low-grade diseases due to their likeness; they are usually coupled together as CLL/SLL. The distinction for the grouping of NHL is made by laboratory tests identifying proteins on the surface of the B cells. CLL/SLL is the most common form of lymphoproliferative disorder in the Western countries, occurring mostly in the elderly [1, 2].

Interestingly, an increased risk for the coexistence of a second malignancy, of epithelial and mesenchymal origin, has been reported in patients with CLL/SLL, for example, in lung cancer [3] or bladder and prostate cancers [4]. The development of a second malignancy was comparable in patients without or with chemotherapy [5]. Moreover, melanomas, nonmelanoma skin cancers, as well as oral cavity, pharynx, prostate, and kidney malignancies may coincide with CLL/SLL [6]. Finally, uncommon malignant tumors, Kaposi sarcoma, and Merkel cell carcinoma have also been documented along with CLL/SLL [7–9]. There are no case studies reporting the coexistence of CLL/SLL with primary human endometrial cancer, although a profound epidemiologic data search revealed a rare coincidence of CLL/SLL with gynecological neoplasms [e.g., 5, 7, 9, 10].

Herein, we present an unusual case of type I (endometrioid-type) uterine cancer with CLL/SLL in a 58-year-old woman. We briefly discuss the coincidence of CLL/SLL with various gynecological neoplasms based on a careful literature review.

Clinical Report

Patient

A 58-year-old woman (G3P3, last menstruation was 4 years ago) was admitted to the 2nd Department of Gynecology, Lublin Medical University, Lublin, Poland, in June 2017, due to abnormal uterine bleeding and extended endometrial thickness (19 mm in diameter). After physical examination, repeated transvaginal ultrasound scans, and an endometrial biopsy, moderately differentiated subtype I (according to the Bokhman classification) uterine cancer was diagnosed. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy. The operation was performed without complications, and the tumor was staged as IIIc based on the revised surgical-patho-

logical FIGO classification. Final pathological assessment revealed a uterine moderately differentiated adenocarcinoma of endometrioid subtype deeply infiltrating the myometrium as well as the uterine cervix. Three intramural leiomyomas were detected. No pathological abnormalities in the adnexa were reported. Surprisingly, CLL/SLL was simultaneously diagnosed in all pelvic and para-aortic lymph nodes that had been removed. The patient was discharged on day 7 and she was forwarded to the Oncology Center of Lublin, Lublin, Poland, for adjuvant chemotherapy and radiotherapy. She is still on follow-up.

Pathological Findings

The uterus was enlarged, measuring 120 × 120 × 90 mm. Three intramural leiomyomas were found within the uterine corpus (50, 50, and 35 mm in diameter, respectively). The epithelium was smooth with local congestions. A white-grey fragile papillary infiltration (85 × 45 × 70 mm in size), which filled the uterine cavity and went down to the canal of the uterine cervix, was demonstrated. The infiltration exceeded 50% of the uterus, but it did not reach the perimetrium.

Microscopically, the tumor was diagnosed as endometrioid G2 endometrial adenocarcinoma of subtype I (according to Bokhman). There was a myometrial infiltration of the uterus, and the uterine cervix was also remarkably infiltrated. Lymphatic infiltration was found in the endometrium, myometrium, and uterine cervix. No malignant cells were found in the adnexa or in the parametrium on both sides. CLL/SLL was detected on both sides in all iliac and peri-aortic lymph nodes dissected.

Immunohistochemistry

Clusters of small lymphocytes were scattered among the peri-aortic and common iliac lymph nodes, and a detailed immunohistochemical staining was performed (Fig. 1a–f). Staining reactions were as follows: CD45 (++), CD20 (+), CD3 (–/+), CD19 (+), CD23 (+), CD5 (+), and CD34 (+). Proliferative activity, assessed by MIB-1 proliferative index immunostaining, reached 18%.

Discussion

A comprehensive literature review showed various malignancies coexisting with CLL/SLL [5–11]. For example, CLL/SLL has been reported coincidentally with adenocarcinoma of the stomach, kidney, breast, colon, liver, and lung [3, 10–12]. Based on our knowledge, this is the first study reporting the coexistence of endometrioid-type G2 endometrial cancer with CLL/SLL.

We diagnosed these 2 malignancies, CLL/SLL with endometrioid-type endometrial cancer, simultaneously and accidentally (i.e., CLL/SLL) during our management. We may apply the criteria for multiple primary malignancies, firstly presented in 1932 by Warren and Gates [13]. They are still appropriate. Multiple primary malignancies are uncommon, and case studies reporting such phenomena are, in general, seldom published [4, 12, 14].

In the literature, Tsimberidou et al. [5] reviewed the data (1985–2005) from the University of Texas, M.D. Anderson Cancer Center, USA, reporting 2,028 patients suffering from CLL/SLL. Interestingly, 324 (16%) of them had a history of coexistence with another malignancy, and 227 (11.2%) developed a second cancer during the follow-up. The risk of a second malignancy in patients with CLL/SLL was increased 2.2-fold compared to the risk for a healthy population [5]. Schöllkopf et al. [6] evaluated the records of 12,373 patients diagnosed with

CLL/SLL between 1943 and 2003. Neoplasms were found in 1,105 cases, 20 of them originated from the female genital tract (4 from the uterine cervix, 7 from the uterus, 8 from the ovary, fallopian tube, and broad ligament, and a tumor with no specific localization). The standardized incidence ratio for all malignancies combined was 1.59 (95% CI 1.5–1.69), ranging from 1.63 (95% CI 1.44–1.85) in the first year after the diagnosis of CLL to 1.8 (95% CI 1.56–2.08) in the period more than 10 years after the primary diagnosis. The risk for the development of gynecological neoplasms in women with CLL was lower (standardized incidence ratio = 0.64) [6]. Dong and Hemminki [9] analyzed the site-specific risk of second primary malignancies in 53,159 hematolymphoproliferative disorder cases diagnosed between 1958 and 1996. They used the Swedish Family-Cancer Database. The gynecological cancers were diagnosed in only 40 women with hematolymphoproliferative disorder during this period, of which 12 originated from the endometrium [9]. Mudie et al. [10] analyzed a cohort of 2,456 patients with NHL below the age of 60 years treated between 1973 and 2000. There were no endometrial cancers coexisting with NHL in their cohort, although 3 gynecological neoplasms were finally diagnosed (2 from the cervix and 1 from the ovary) [10]. Based on the review of cohort literature data, the coexistence of CLL/SLL with primary human endometrial cancer is a rare event, in general reported accidentally.

The management of CLL/SLL and patients' prognosis depend on the age of the patient, patients' general condition, concomitant diseases, therapeutic aims, prognostic factors as well as the clinical advancement of the neoplasm. There are 2 possibilities of treatment protocols: allogeneic hematopoietic stem cell transplantation or chemo-/immunochemotherapy [2, 15]. If the patient does not fulfill the criteria to start treatment according to the International Workshop on Chronic Lymphocytic Leukemia, follow-up observation remains an option. In general, the management of a secondary neoplasm does not differ from a cancer that appears de novo, but the burdens related to the primary type of neoplasm must be taken into account [2, 15].

Conclusion

The coexistence of CLL/SLL with various gynecological malignancies, especially primary human endometrial cancer, is a rare entity. In general, the detection of both tumors simultaneously is accidental, and the management should not be different from the situation in which a malignancy appears de novo.

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Statement of Ethics

The Independent Ethics Committee of Lublin Medical University, Lublin, Poland, approved the study. Written informed consent was obtained from the patient for publication of this case study and any accompanying images.

Disclosure Statement

The authors report no conflict of interest.

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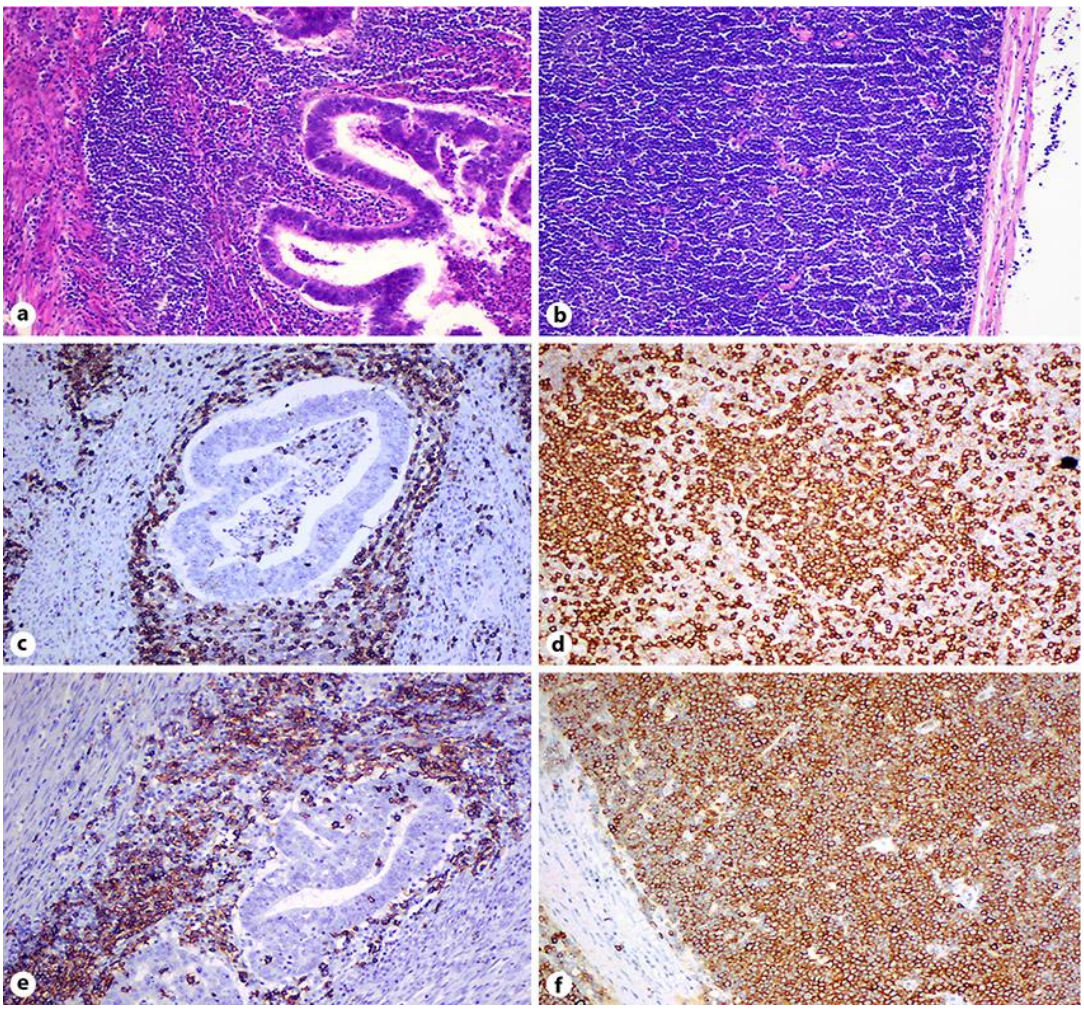

Fig. 1. **a** Endometrioid-type moderately differentiated endometrial cancer with infiltration of small lymphocytes. HE. **b** Lymph node with chronic lymphocytic leukemia/small lymphocytic lymphoma. HE. Lymphocytic infiltration was found immunohistochemically positive for CD5 (**c**, primary tumor; **d**, lymph node) as well as for CD20 (**e**, primary tumor; **f**, lymph node). ×200.