

**TWO CLINICAL CASES OF SECONDARY NEOPLASIA AFTER  
REMISSION OF HODGKIN'S DISEASE**
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**Summary**

Hodgkin's disease is one of the most common lymphomas in young people. In such cases, long-lasting hematological remissions are achievable using therapeutic regimens, including combined radiotherapy and chemotherapy. This publication aims to present clinical cases from our practice in patients with Hodgkin's disease in whom the occurrence of second neoplasia is probably causally related to the treatment of Hodgkin's lymphoma. We present two clinical cases of women with established secondary neoplasia (breast carcinoma, diffuse large B cell lymphoma) 20 years after treatment for Hodgkin's disease had been completed. The probability of developing another neoplastic disease, leading to increased mortality in these patients, requires updating the recommendations for secondary prevention in oncology.

**Keywords:** Hodgkin's disease, secondary tumors, radiotherapy

**Introduction**

According to the International Agency for Research on Cancer (IARC), 80,000 cases of Hodgkin's disease (HD) were diagnosed worldwide in 2018 [1]. The disease is potentially curable, with a reported 5-year survival rate in 80-86% of cases [2, 3, 4]. Developing another malignancy years after treatment has been completed is one of the reasons for increased mortality in these patients. Secondary tumors have been reported using chemotherapy containing alkylating agents and when this therapy is combined with radiotherapy. The most common hematologic neoplasias are acute myeloid leukemia, myelodysplastic syndrome, and non-Hodgkin's lymphoma. Solid tumors include thyroid cancer, soft tissue sarcoma, lung cancer, colorectal cancer, and breast cancer.

According to the National Cancer Institute, as of 2017, the median age of breast cancer diagnosis in the general population is 62 years [5]. The age cutoff for this tumor type is

significantly lower in young women treated earlier for Hodgkin's disease. Risk factors such as familial predisposition, genetic disability, hormonal status, the toxic effect of the local radiotherapy performed are likely to play a leading role in developing breast cancer among this group of patients.

The reasons for the increased risk of non-Hodgkin's lymphoma (NHL) are unclear [6], although the problem has been discussed since the 1970s. The reported cumulative risk of developing NHL is 1.5% per 15 years [7]. A report by V. Krikorian J et al. (1979), when the treatment regimen included Mechlorethamine hydrochloride, Vincristine, Procarbazine, Prednisolone (MOPP) or Procarbazine, Melphalan and Vinblastine (PAVe), concluded that the abdomen and gastrointestinal tract were more commonly affected in cases of NHL occurring after complex treatment. Such characteristics, however, were considered unusual for HD [8]. The trend in reducing late sequelae of treatment for HD has been towards using smaller volumes and lower doses of radiation, less toxic polychemotherapy (PCT) regimens. Nevertheless, the effect of these changes on the risk of second cancers is still unknown [9].

We present two clinical cases from our practice of proven secondary neoplasms after a long period of completed therapy for HD. The diagnosis was based on clinical symptoms associated with a second neoplasm rather than regular screening examinations in both cases.

### **Case 1**

DG, a 23-year-old woman, was diagnosed with Hodgkin's disease nodular sclerosis in 1999 after an excisional biopsy of a cervical lymph node. She was staged with imaging as clinical stage II B due to the involvement of the cervical and mediastinal lymph nodes. Three courses of Adriamycin, Bleomycin, Vinblastine, Doxorubicin (ABVD) regimen in conventional doses, supradiaphragmatic radiotherapy at a dose of 36 Gray, and three more cycles of the same therapeutic regimen followed. After a reported remission, the patient was followed up at the hematology department for four years. Two normal pregnancies with live-born, healthy children followed. In June 2019, a biopsy was

performed on a newly diagnosed painless tumor in the right breast and demonstrated G3 invasive ductal carcinoma. A mastectomy was performed, and 11 lymph nodes were removed. No metastases were found. The patient was staged as T1cN0M0. The tested receptor status for estrogen, progesterone and human epidermal growth factor receptor two was negative, Ki67>80%. In conventional doses, six courses of PCT, including cisplatin and paclitaxel, were performed, resulting in disease remission. Follow-up examinations were scheduled at the regional cancer dispensary.

### **Case 2**

A 31-year-old woman was diagnosed with *nodular sclerosing Hodgkin lymphoma* in July 2000 after a biopsy and histologic examination of an enlarged right supraclavicular lymph node. The patient - a smoker, had no family history of malignancy. Her past medical history included tracheobronchial lymph node tuberculosis in 1996 and viral hepatitis type B. The patient was evaluated using laboratory and computed tomography studies because of the evidence of enlarged anterior mediastinal lymph nodes on the right and supraclavicular lymphadenomegaly. According to the Ann Arbor staging system, she was diagnosed with clinical stage II B. Treatment was administered with ABVD (three courses), supradiaphragmatic 36Gray (upper Kaplan) radiotherapy, followed by three courses of ABVD. One month after completing the last therapy, a restaging scan was performed. Based on a comprehensive evaluation of the physical status, imaging, and laboratory studies, remission of the disease was considered achieved. The patient was followed up regularly in outpatient care for five years. In June 2021, she complained of general weakness and heaviness in the abdomen. Abdominal ultrasonography revealed a tumor formation in the right ovary. The patient had been in menopause since 2000. Surgical treatment was performed.

Both ovaries were removed intraoperatively because of their destruction by a nodular tumour measuring 9 cm in the left ovary and 3 cm in the right. Macroscopy of the uterus, endometrium, cervix, and omentum did not reveal pathological abnormalities. Immunohistochemical examination of the removed tumor formation

revealed diffusely organized proliferation of medium/large atypical lymphoid tissue with variable similarity to transformed immunoblasts and centroblasts expressing CD20, BCL-2, and negative for CD10 and C-myc. Ki-67 >60% positive. It was assumed to be extranodal (ovarian) diffuse B-cell lymphoma. A PET scan and laboratory investigations conducted three months after surgery revealed no active disease and pathological substrate evidence. The patient was stratified as low risk based on the revised International Prognostic Index (R-IPI). Regular follow-up examinations by an oncologist and hematologist were recommended.

## Discussion

As of 1999-2000, standards of care for young HD patients included a combination of ABVD and COPP regimens with radiotherapy. Depending on the stage of the disease (Ann Arbor staging system), the number of planned courses of PCT is determined and the areas to be irradiated (supradiaphragmatic or subdiaphragmatic). Early side effects of chemotherapy regimens are usually short-term and controllable, in contrast to late side effects, such as secondary neoplasms, reported more frequently with the combination of chemo- and radiotherapy. In the two clinical cases we presented, a second neoplasm was diagnosed 20 years after the end of treatment for HD. According to literature data, the risk of breast cancer starts to increase 5-9 years after the end of treatment, peaks 15-19 years after treatment, and persists up to 40 years of follow-up [10].

The significance of genetic factors for increased risk of breast cancer in women undergoing radiotherapy for HD is unclear [11]. A study by Amit Sood et al. reported a higher risk of developing second neoplasia in patients with HD and a family history of malignancy among first-degree relatives [12]. There was no family history of malignancy in the two clinical cases we present in this report. One hypothesis for the higher incidence of breast cancer in women who underwent radiotherapy for HD in adolescence is related to the effect of radiotherapy on the mammary gland when breast tissue is proliferating [13,14]. Another risk factor is ovarian function. Shorter (<10 years) preserved ovarian hormonal

function after radiotherapy is associated with a lower risk of developing breast cancer [15]. In a retrospective study by Kathleen Horst et al., including 65 women with available histological examination confirming breast cancer after radiotherapy for HD, the authors looked for similarities between histological subtypes of breast cancer in this group compared with breast cancer developed in women without prior radiotherapy. Following immunohistochemical testing for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in patients with proven invasive cancer, the authors reported a higher incidence of triple-negative (HR-/HER2-) variants among the group with a history of prior radiotherapy [16]. In the cases we present, the immunohistochemical result was similar to the data from the study mentioned above. Non-Hodgkin's lymphomas are mentioned in the hematologic neoplasias, although less frequently compared to solid tumors. In 2010, Andreas Engert et al. published the results of a multicenter clinical trial registered as NCT00265018, which aimed to determine the optimal effective dose of radiation and chemotherapy in untreated, low-risk patients with early-stage Hodgkin's disease. With a median follow-up of 90 months and a total number of patients of 1190, 55 patients had secondary neoplasia. These included 38 solid tumors, 15 non-Hodgkin's lymphomas, and 2 cases of acute myeloid leukemia [17]. One year later, Anthony J. Swerdlow et al. published a study on an impressive cohort of 5798 HD patients treated and followed up from 1963 to 2001. According to these authors, the risk of developing NHL was higher when radiotherapy was combined with chemotherapy than in those with chemotherapy alone [6].

Current trends in the treatment of Hodgkin's disease are related to more accurate staging and monitoring of patients with PET scanning. Adequate risk stratification to the diagnosis and selection of the most effective and, at the same time sparing therapeutic approach, aim to minimize early and late sequelae of treatment. Also, given the importance of the problem in patients with HD in the long run, it should not be forgotten that the basis of medical statistics is good medical registration.

## Conclusion

Given the late effects of the applied therapy, achieving durable remissions in patients with Hodgkin's disease does not contradict the need for long-term follow-up. Regular check-ups, including physical status, laboratory tests, instrumental diagnostics (ultrasonography, particularly the breast), and MRI, are sparing investigations. A haematologist and a general practitioner could discuss follow-up after HD treatment has been completed. Once a battle is won to achieve long-lasting remissions, there is probably an opportunity to win the war through adequately planned screening tests and coordination between medical professionals.

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