Diffuse large B-cell lymphoma in a patient after allogeneic haematopoietic stem cell transplantation due to Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is a cancer which is characterised by the presence of Reed-Sternberg (RS) and Hodgkin's cells in the cancerous infiltrations. Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in adults, and it belongs to a group of lymphomas which are extremely aggressive and require immediate treatment implementation. We present the case of a 25-year-old male patient diagnosed with Hodgkin's lymphoma who underwent megachemotherapy supported by allogeneic transplantation of haematopoietic stem cells as the second-line treatment. However, three years after the transplantation, the patient was diagnosed with DLBCL, which was originally found in bones. It is a very rare location of non-Hodgkin's lymphomas. The rarity of the presence of lymphomas in bones, as well as the diversity of the clinical course of the disease, makes it difficult to establish the rules of treatment.

Key words: diffuse large B-cell lymphoma, Hodgkin's lymphoma, haematopoietic stem cell transplantation, chemotherapy.

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Introduction

Hodgkin's lymphoma (HL) is a cancer of the lymphatic system which is characterised by the presence of malignant Reed-Sternberg (RS) and cells of Hodgkin's lymphoma [1]. The estimated morbidity of Hodgkin's lymphoma in the western part of the world is 2–4 cases per 100,000 inhabitants. Hodgkin's lymphoma is most common among adult men [2]. Diagnosis of the disease is established by means of histopathological tests of the lymph node or tissue. In order to establish a diagnosis, RS cells should be found in the preparation [3]. It is believed that currently the lymphoma has the highest cure rate. Approximately 80% of cases are cured, normally after first-line treatment. However, some patients experience recurrences of the disease [4].

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma, and it constitutes approximately 30–40% of all diagnosed lymphomas [5]. This is an aggressive lymphoma and, if not treated, causes rapid death. The diagnosis is based on a histopathological test which shows a diffuse infiltration with a blurred structure of a lymphatic node or an infiltration of an involvement of an extralymphatic site. At present, it is estimated that it is possible to cure over 50% of cases [6].

In the case presented below, the patient, who was previously treated for Hodgkin's lymphoma, was then diagnosed with diffuse large B-cell lymphoma of bones.

Case description

The patient at the time of HL diagnosis (June 2002) was a 25-year-old male Caucasian. The described man enrolled at the general outpatient clinic due to a painless lymphadenopathy in the area of the trachea, which gradually transformed into an infiltration of this region. Fine-needle aspiration yielded purulent material. The performed surgical incision was complicated by the creation of a non-healing purulent fistula. Despite frequent irrigation and the implementation of antibiotics, the local state was not improved. In November 2002, magnetic resonance imaging (MRI) demonstrated a polycyclic, solid change with abscess characteristics, which caused tightness of the trachea with a narrowing of the lumen and left-sided displacement as well as a displacement of veins and arteries of the mediastinum. In the

tissue taken in the course of cardiothoracic surgery, Hodgkin's lymphoma (nodular sclerosis type II, NS II CD15–/CD30+) was diagnosed. The patient was directed to the Chemotherapy Department in order to implement treatment. Submandibular lymph nodes and lymph nodes in the neck were swollen up to 1 cm and in the area of groins up to 1.5 cm. Computed tomography (CT) demonstrated a node mass (40 mm × 33 mm × 80 mm) in the mediastinum, paratracheal lymphadenopathy (11 mm × 12 mm × × 8 mm) and cancerous infiltration of the spleen (110 mm × × 55 mm). Neither swollen lymph glands in retroperitoneal space nor diffuse infiltrations in the bone marrow biopsy were found. As a result of staging, before the implementation of the treatment, the clinical extent of the cancer was established first (adverse prognostic factors: male, bulky disease, NS II). On the basis of the aforementioned assessment, the patient was qualified for ABVD (Adriamycin, bleomycin, vinblastine and dacarbazine) chemotherapy and radiotherapy at the site of the disease. In the middle of January 2003, the treatment was implemented. Starting with the second course of chemotherapy, due to neutropenia, the patient required implementation of G-CSF (granulocyte colony-stimulating factor). As part of restaging, imaging examinations were conducted (CT of the nasopharynx, neck, chest and abdominal cavity, ultrasonography of the abdominal cavity and peripheral lymph nodes) and the image of a complete remission was achieved. The decision to continue the treatment with up to six courses of ABVD was taken. The treatment was completed in June 2003. In July 2003, the patient was qualified for radiation of the mediastinum. The patient received a dose of 3060 cGy at 180 cGy per fraction, without any complications, and completed the treatment in August 2003. The patient was under ambulatory observation for over 3 years. In the Laryngological and Pulmonological Clinic, the patient was not diagnosed with any aberrations.

In November 2007, as well as persistent cough, the patient experienced a swallowing disorder. In ultrasonography (USG) of the neck and thyroid gland, a hypogenic lymph gland (25 mm × 14 mm) and a solid change (16 mm × 9 mm) on a lower pole of the right lobe were demonstrated. The histopathological test of the lymph node confirmed the recurrence of the disease. Another CT on the right site from the carotid vessels at the lower part of the neck exposed a lymph gland (22 mm × 21 mm × × 30 mm) and infiltrative changes (37 mm × 57 mm × × 42 mm) from the level of the middle pole of the thyroid lobes, paratracheal with a tightness and a shift of the trachea to the left side, paraspinally on the right side and centrally in the posterior mediastinum. Similar changes (37 mm × 40 mm × 60 mm) were visible on the levels Th4–Th5, which compressed and shifted the oesophagus. The spleen and the lymph glands remained unchanged. After consultation with the Centre of Transplantology, it was decided to implement a dihyroxyacetone phosphate (DHAP) chemotherapy regimen (dexamethasone, cytarabine and cisplatin) prior to autologous stem cell transplantation. After two cycles of the treatment, restaging was conducted and a total regression of the peripheral lymph nodes and a 50% reduction of diffusive changes in the

mediastinum were observed. Consequently, another two cycles of DHAP were administered. From the third cycle, taking neutropenia into consideration, implementation of G-CSF was essential. In March 2008, after four courses of DHAP, the response to the treatment was as follows: a partial remission in the mediastinum (50% regression) and a complete regression of nodal lesions. Double cell mobilisation with a three-month interval, performed due to the planned transplantation, did not bring a satisfactory collection. Hence, it was decided to conduct an allogeneic transplantation from a related donor – a brother – in August 2008.

From September 2008, the patient was under observation. In PET-CT scans a complete remission was observed. Since the end of 2009, pain in the area of the right hip joint appeared. A PET-CT scan performed in January 2010 revealed bone remodelling in the area of the right femoral head, and in MRI an image was obtained which indicated avascular necrosis. In October 2010, hip arthroplasty was conducted. Starting from the end of 2011, generalised bone pain with particular intensity in the pelvis and the left hip joint appeared. In a PET-CT (positron emission tomography–computed tomography) scan performed in December 2011, changes in the skeletal system were seen in the form of an active growth process (infiltrations with a destruction of the right ilium, part of the head, greater trochanter and proximal extremity with a suspected impacted fracture of this area). Figure 1 presents representative PET-CT transaxial images of the lesions (yellow arrows indicate bone destruction). Radiation with a single 8 Gy fraction was implemented to the pelvis area. At the same time, the pathological fracture of the neck of the left femur was surgically wrapped and a sample from the greater trochanter of the left femur was taken for histopathological testing. DLBCL was diagnosed. Immunohistochemical analysis revealed the following cellular immunophenotype: CD20(+), LCA(–), CD3(–), CD15(–), CD30(–), EMA(–), MPO(–), CD43(–), CD34(–), and Ki67(+) in 80% of cells.

Further diagnostics performed in the Haematology Department revealed no swollen lymph nodes. Computed tomography of the femur and ilium bones confirmed the changes observed in the PET-CT scan. Histopathological assessment of the puncture specimen did not demonstrate any infiltrations of the lymphoma. On the basis of the clinical image, the stage of the disease was classified as Ann Arbor stage 4. In March 2012, hyper-CVAD (course A: cyclophosphamide, vincristine, doxorubicin, dexamethasone, and course B: methotrexate, cytarabine) treatment was implemented. After the third course of chemotherapy, septic shock appeared due to severe pancytopenia. The chemotherapy was discontinued. In the control PET CT scan, in September 2012, the aforementioned changes of proliferative nature were not visible.

Discussion

Despite the high effectiveness of the first-line treatment, we can observe a failure of the treatment (either recurrence or resistance) in 15% of patients in an early stage and 30% of patients in an advanced stage of Hodgkin's
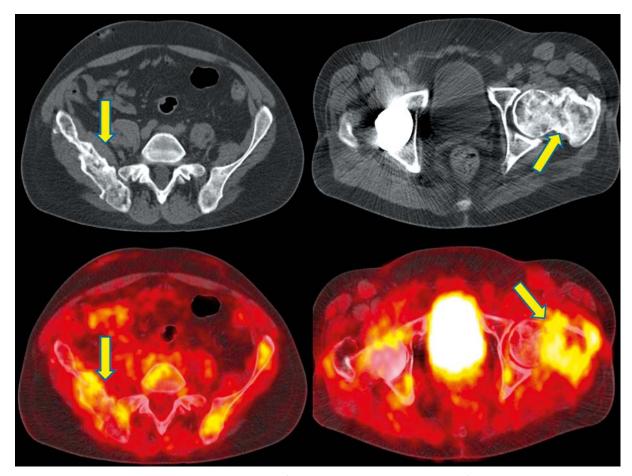
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Fig. 1. Representative PET-CT transaxial images of the lesions (yellow arrows indicate bone destruction)

lymphoma [7, 8]. Currently, in such cases the standard procedure is to implement a phase II rescue chemotherapy and mega-dose chemotherapy supported by autologous haematopoietic stem cell transplantation [9]. In the described case, such a treatment was chosen; however, due to the failure of stem cell collection, it was decided to conduct an allogeneic transplantation from a related donor: in this case, a brother. Despite the fact that allogeneic haematopoietic stem cell transplantation (alloHSCT) in patients with a diagnosis of Hodgkin's lymphoma raises controversies due to high transplant-related mortality (TRM), in the described case it was possible to avoid complications connected with this procedure. Nevertheless, the introduction of reduced intensity conditioning (RIC) allowed a reduction in transplant related mortality. Analysis of the data demonstrate that RIC with alloHSCT enables long survival in 20–30% of patients [8–10].

In the discussed case, less than three years after the treatment was completed, the symptoms of DLBCL appeared, primarily in bones. It is a very rare location of non-Hodgkin's lymphomas. It is estimated that they constitute approximately 7% of all bone cancers and 5% of all extralymphatic lymphomas [11]. The most common histological subtype is DLBCL, accounting for about 80% of cases in Western countries [12, 13]. The rarity of the presence of lymphomas in bones, as well as the diversity of the clinical course of the disease, makes it difficult to establish the rules of the treatment. It seems that in order to limit the size of the changes, the optimal solution would be a combined treatment of a radiotherapy and chemotherapy [14]. In this case, initially radiotherapy was implemented, which was complemented with hyper-CVAD. Despite the complications, the treatment improved the general state of the patient, and almost all complaints were reduced.

Prognosis of such a case is extremely difficult due to its rarity. A helpful diagnostic method may be the assessment of SPF (S-phase fraction). Lackowska *et al.* revealed that the level of SPF is related to the reaction for DLBCL treatment and to the frequency of recurrences after reaching total remission [15]. It is worth considering SPF assessment in all clinical situations similar to the described case.

A significant problem in the treatment of HL is a long-term complication in the form of secondary cancers. During many years of observation, an increase of acute non-lymphoblastic leukaemia and myelodysplastic syndrome (MDS) incidence has attracted our attention. The possibility of developing a solid cancer significantly increases. In one of the research projects conducted at two research facilities in Holland in a group of 1261 individuals treated due to HL, it was demonstrated that a cumulative risk of secondary cancers after a 28-year observation is 18.8%, out of which 14.4% constitute solid cancers, 3%

non-Hodgkin's lymphomas and 1.5% acute non-lymphoblastic leukaemia. The method of treatment also influenced the type of secondary cancer. Solid cancers (e.g. lung or gastric cancer) were more frequent in patients who had undergone radiotherapy; however, secondary haematological malignancies more often accompanied systemic chemotherapy. Furthermore, haematological malignancies occurred the most often 9 years after the treatment, and solid cancers were observed 20 years after the treatment [7]. The procedure of treatment with the use of high-dose chemotherapy and auto-HSCT also increases the incidence of secondary haematological malignancies in a significant way (MDS/AML) [8]. Due to the mentioned reasons, there is a necessity to monitor patients who have been treated for HL for secondary cancers. It requires establishing new standards of screening tests in this group of patients.

In the presented situation, we should also pay attention to a particular clinical situation, namely, post-transplant lymphoproliferative disease (PTLD). It constitutes one of the most serious transplant-related complications. PTLD is a spectrum of lymphoid hyperproliferative states that may be observed in solid organ and bone marrow transplant recipients [16]. The majority of cases of post-transplant lymphoma (PTL) are Epstein-Barr virus (EBV)-positive [17]. Iatrogenic immunosuppression leading to primary EBV infection or reactivation of latent EBV infection is followed by polyclonal expansion of B cells. These cells are susceptible to molecular aberrations driving a malignant growth [18]. It should also be emphasised that the infection with EBV plays a crucial role in the development of Hodgkin's and non-Hodgkin's lymphomas [19]. The current scenario for HL is that the expression of viral latent membrane protein 1 (LMP-1) and LMP-2A may prevent apoptosis by mimicking CD40 and BCR signalling, respectively [20, 21]. LMP-1 plays also a crucial role in the transformation of B-lymphocytes by EBV into immortalised human primary B cells [22] by activating NF-κB and other anti-apoptotic factors [23].

It seems that the acceptance of the primary aetiology of the lymphoma of the bone was fully justified in the described patient.

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Authors declare no conflict of interest.

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