Early Detection of Richter's Transformation: Stable Disease with Dose-Reduced Gemcitabine and Local Radiation

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Key Words

Richter transformation · Hodgkin's disease variant · Gemcitabine

Summary

Background: The occurrence of Hodgkin's lymphoma (HL) as a second aggressive lymphoid malignancy (known as Hodgkin's disease variant of Richter's transformation) is rarely observed. Response rates, even with highly aggressive therapy such as stem cell transplantation, are limited, ranging from 4 to 43%, and the medium survival time ranges from 5 to 8 months. **Case Report:** A 72-year-old patient with a history of chronic lymphatic leukemia (CLL) was admitted with thoracic back pain and assumed progression of the CLL. The patient showed no fever, night sweats or weight loss. A computed tomography (CT) scan confirmed the progression of axillary and cervical lymph nodes. In addition, an intraspinal infiltration at the 8th thoracic vertebra (Th8) was detected. Surprisingly, histology of an extirpated lymph node demonstrated the existence of 2 tumors in the same lymph node. Infiltrates of small lymphocytes representing the pre-existing CLL (CD5-, CD20-, CD23-positive) coexisted with Reed-Sternberg Hodgkin's cells (CD30-, CD15-positive). Chemotherapy was started, combined with palliative radiation of vertebrae Th7–Th10. 12 months after diagnosis of Richter's transformation the patient is still alive without any progression of the underlying disease. **Conclusion:** We present a unique case of a Hodgkin's disease variant of Richter's transformation and CLL in the same lymph node, which was detected early because of spinal infiltration and was subsequently stabilized with reduced-dosage gemcitabine and local radiation. Additionally, we show unique pictures of 2 tumors coexisting in the same lymph node.

Schlüsselwörter

Richter-Transformation · Hodgkin-Variante · Gemcitabin

Zusammenfassung

Hintergrund: Das Auftreten eines Hodgkin-Lymphoms als zweite aggressive, bösartige, lymphoidzellige Erkrankung (bezeichnet als Hodgkin-Variante einer Richter-Transformation) wird sehr selten beobachtet. Selbst mit Hochdosis-Regimen bewegen sich die Ansprechraten etwa zwischen 4 und 43%. Die mittlere Überlebenszeit beträgt 5–8 Monate. **Case Report:** Wir berichten über einen 72-jährigen Patienten, der bei bekannter chronischer lymphatischer Leukämie (CLL) aufgrund zunehmender Schmerzen im Bereich des Rückens unter der Annahme eines Progresses der CLL stationär aufgenommen wurde. Fragen nach Fieber, Nachtschweiß und Gewichtsverlust wurden verneint. Computertomogramm (CT)-Aufnahmen zeigten eine Größenzunahme axillärer und zervikaler Lymphknoten. Zudem zeigte sich eine intraspinale Raumforderung in Höhe des achten Brustwirbels (Th8). Histologisch konnten in der durchgeführten Lymphknotenbiopsie 2 Tumore in ein und demselben Lymphknoten festgestellt werden. Es zeigten sich Infiltrate der vorbestehenden CLL (CD5-, CD20-, CD23-positiv) in Koexistenz mit Reed-Sternberg-Hodgkin-Zellen (CD30-, CD15-positiv). Eine Chemotherapie in Kombination mit lokaler Bestrahlung wurde begonnen. 12 Monate nach der Erstdiagnose einer Richter-Transformation ist der Patient am Leben ohne Zeichen von Progress. **Schlussfolgerung:** Wir präsentieren hier das Auftreten eines Morbus Hodgkin mit einer CLL als eine seltene Variante einer Richter-Transformation, die durch die frühe Diagnosestellung mit subtherapeutischer Dosis von Gemcitabin und lokaler Bestrahlung nun über 12 Monate stabilisiert werden konnte. Zudem können wir anhand dieses Falles ein Bild zweier Lymphome in ein und demselben Lymphknoten zeigen.

Introduction

Richter's transformation (Richter's syndrome, RS) represents rare cases of high-grade lymphoma in patients with pre-existing chronic lymphocytic leukemia / small lymphocytic lymphoma. The occurrence of Hodgkin's lymphoma (HL) as a second aggressive lymphoid malignancy in RS (so-called Hodgkin's disease variant of Richter's transformation) is very uncommon. The mechanisms of the alteration of chronic lymphatic leukemia (CLL) to RS are not yet fully understood. Microorganisms, such as *Epstein-Barr virus*, may trigger RS, and an association with fludarabine treatment [1–4] has also been reported. Characteristic signs of RS are systemic symptoms (e.g. fever, weight loss and/or night sweats), rapid increase in the size of secondary lymphoid organs and elevated lactate dehydrogenase (LDH). Rarely, RS presents with extranodal involvement. Response rates, even with highly aggressive therapy including stem cell transplantation, are limited, ranging from 4 to 43%, and the medium survival time ranges from 5 to 8 months [1].

Here, we present the case of a patient with RS which was detected unusually early because of thoracic spinal infiltration. The patient's disease was stabilized by a reduced dosage of gemcitabine and local radiation. The diagnosis was established by histology from a lymph node that showed the unique coexistence of both B-CLL and HL.

Case Report

A 72-year-old patient with a history of CLL was admitted because of thoracic back pain that was presumed to be a result of progressive disease. The initial diagnosis of CLL was made in 1994. The patient had received prednisone (75 mg on days 1 and 15, 50 mg on days 2 and 16, and 25 mg on days 3 and 17) and chlorambucil (0.4 mg/kg on days 1 and 15) between 1994 and 2002, fludarabine (25 mg/m²) in 2002, 5 cycles of a combination therapy with fludarabine (25 mg/m²), cyclophosphamide (250 mg/m²) and rituximab (375 mg/m²) between 2003 and 2004, and 6 cycles of R-CHOP (rituximab 375 mg/m², cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², daunorubicin 50 mg/m², prednisolone 100 mg) between 2004 and 2005, together with involved field radiation of an abdominal bulk with good clinical responses.

At the time of admission, major complaints were severe thoracic paravertebral back pain, fatigue and energy loss. The patient did not suffer from night sweats, fever or weight loss. Physical examination revealed enlarged cervical and axillary lymph nodes. Laboratory values on admission to the hospital included decreased hemoglobin of 11.2 g/dl (reference range (RR) 13–17 g/dl) and a leucocyte count of $4.03 \times 10^3/\mu\text{l}$ with 2% atypical lymphocytes and thrombocytes ($145 \times 10^3/\mu\text{l}$) within the normal range. LDH was marginally elevated to 319 U/l (RR < 248 U/l), serum albumin was decreased at 33.4 g/l (RR 35–55 g/l), and total protein was at 54.2 g/l (RR 66–83 g/l). C-reactive protein was elevated (19 mg/l; RR < 5 mg/l). Other blood chemistry results as well as coagulation studies were all within normal limits. Low serum levels of IgG (401 mg/dl, RR 751–1560 mg/dl), IgM (7.8 mg/dl, RR 46–304 mg/dl) and IgA (28.5 mg/dl, RR 82–454 mg/dl) demonstrated panhypoglobulinemia.

Computed tomography (CT) scans confirmed the progression of axillary and cervical lymph nodes. In addition, an intraspinal infiltration at the 8th thoracic vertebra (Th8) was detected (fig. 1). Consequently, an axillary

Fig. 1. CT scan of a thoracic spinal infiltration of Hodgkin's lymphoma. **A** Infiltration at Th8. White arrows show lymphoma masses infiltrating the left intervertebral foramen. **B** Infiltration at Th2/3. White arrows show lymphoma masses infiltrating the right intervertebral foramen.

lymph node extirpation was initiated with the hypothesis of RS, and pain therapy was started. Surprisingly, histology of the lymph node demonstrated the existence of 2 tumors in the same lymph node. Infiltrates of small lymphocytes representing the pre-existing CLL (CD5-, CD20-, CD23-positive) coexisted with Reed-Sternberg cells (CD30-, CD15-positive) (fig. 2). Therefore, chemotherapy according to the CEVD-protocol (lomustine 80 mg/m², etoposide 120 mg/m², vindesine 3 mg/m², dexamethasone 3 mg/m² days 1–8, and 1.5 mg/m² days 9–26) [5] was started, together with palliative radiation of vertebrae Th7–Th10.

During the follow-up, chemotherapy had to be stopped on day 22 of the first cycle because of pancytopenia with a hemoglobin of 8.5 g/dl, a leukocyte count of $1.32 \times 10^3/\mu\text{l}$ and a platelet count of $32 \times 10^3/\mu\text{l}$. By that time, isolated treatment of thoracic infiltration at Th8 was insufficient to prevent further progression of mediastinal, thoracic and inguinal lymphomas as indicated by an increasing serum LDH of up to 900 U/l (RR < 248 U/l). A new intraspinal infiltration at the Th2 and Th3 caused severe upper thoracic paravertebral back pain which was controlled after initiation of palliative radiation and opioid pain medication.

Second-line therapy in this palliative setting with expected loss of life was provided with gemcitabine weekly (normal dosage 1,000 mg/m²). A reduced dosage of gemcitabine of 1,300 mg (650 mg/m²) was chosen for the first administration (week 1) because of the extensive pretreatment of the patient [6]. In week 2, a reduction of gemcitabine to 800 mg (40% of the normal schedule with 1,000 mg/m²) was necessary because of reduced leukocytes ($3,800/\mu\text{l}$) and thrombocytes ($90,000/\mu\text{l}$) that were thought to have resulted from toxicity of the combination therapy. After the reduction of gemcitabine to 40% of the normal dosage, no further hematological toxic-

Fig. 2. A Section of an axillary lymph node stained for the CLL marker CD5. The white arrow depicts a diagnostic Reed-Sternberg cell. **B** Staining of the same lymph node for the Hodgkin's marker CD30.

ity > grade 2 according to common toxicity criteria (CTC) occurred during the following 12 administrations.

7 months after diagnosis of RS, a CT scan was performed showing stable disease with a minor reduction in the size of some lymph nodes. 5 months later (12 months after diagnosis of RS), the patient is still alive and in a clinically stable condition, with 4,000 leucocytes/ μ l, 100,000 thrombocytes/ μ l and 11.9 mg/dl hemoglobin, without detectable CLL cells in the peripheral blood.

Discussion

Most commonly, treatment regimens for patients with RS include conventional therapy (e.g. CHOP or its variants), radioimmunotherapy, and high-dose therapy followed by hematopoietic cell transplantation. Thus, patients with RS are generally treated similarly to patients with de novo aggressive

lymphoma, lymphoma patients refractory to cyclophosphamide, vincristine, procarbazine and prednisone (COPP) or HL patients refractory to doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) [5–7].

However, patients who have received numerous pretreatments are normally unable to tolerate conventional treatment. For this reason and because of the age of our patient and the location of the tumor, we decided in the present case to use gemcitabine in combination with local radiation, as suggested in recent reports [6, 9]. With this third line regimen, the disease could be stabilized, and after a dose reduction that was necessary because of hematological toxicity, combination therapy (gemcitabine and local radiation) was well tolerated without hematological and infectious complications. Hence, the treatment employed was successful in this heavily pretreated RS patient.

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