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Concomitant occurrence of Hodgkin variant of Richter syndrome and a lung cancer in a patient with CLL – a case report and review of the literature

Jednoczesne wystąpienie transformacji przewlekłej białaczki limfocytowej do chłoniaka Hodgkina i raka płuca – opis przypadku i przegląd literatury

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Summary

Chronic lymphocytic leukaemia (CLL) is usually stable over months to years however a small proportion of cases may transform to more aggressive types of lymphomas. Development of systemic symptoms such as losing weight, fever or local symptoms such as rapidly growing organomegaly in a patient with CLL suggests transformation to high grade lymphoma known as Richter's syndrome. Similar symptoms can occur in case of second malignancy, which incidence in patients with CLL is 10-20% higher compared to normal population. Here we present a clinical course, diagnostic and therapeutic difficulties in 59-year old patient who simultaneously developed non small cell lung cancer and transformation to Hodgkin lymphoma (HL) 2 years after the diagnosis of CLL. The epidemiology and clinical course of Hodgkin variant of Richter syndrome as well the genetic aberrations possibly shared in development of CLL and lung cancer have been discussed.

Key words: chronic lymphocytic leukemia, Richter's syndrome, Hodgkin lymphoma, second malignancy, oncogenes

Streszczenie

Przewlekła białaczka limfatyczna (CLL) przebiega stabilnie przez okres od wielu miesięcy do wielu lat. U niewielkiego odsetka przypadków może jednak przekształcić się do bardziej agresywnych typów chłoniaków. Pojawienie się objawów systemowych, takich jak utrata masy ciała, gorączka lub miejscowych pod postacią szybko narastającej organomegalii u chorego z CLL budzi podejrzenie transformacji w chłoniaka o wysokim stopniu złośliwości, zwanej zespołem Richtera. Podobne objawy mogą pojawić się w przypadku drugiego nowotworu, którego ryzyko rozwoju u chorych z CLL jest o 10-20% wyższe niż w zdrowej populacji. Poniżej przedstawiamy przebieg kliniczny, trudności diagnostyczne i terapeutyczne u 59-letniego pacjenta, który równocześnie rozwinął niedrobnokomórkowego raka płuca i transformację do chłoniaka Hodgkina (HL) dwa lata po rozpoznaniu CLL. Dodatkowo omówiono epidemiologie i przebieg kliniczny transformacji CLL do chłoniaka Hodgkina, a także aberracje genetyczne występujące wspólnie w rozwoju raka płuca i CLL.

Słowa kluczowe: przewlekła białaczka limfocytowa, zespół Richtera, chłoniak Hodgkina, onkogeny

INTRODUCTION

The course of B-cell chronic lymphocytic leukaemia (CLL) is variable: indolent in about one third of patients never requiring treatment. Approximately one-third represents an initially indolent disorder that progresses and requires therapy within 5 years after diagnosis. In remaining patients CLL is more aggressive disease requiring treatment but disease still maintains its characteristic phenotype (1).

However a small proportion of cases even with an indolent disease may transform to high grade aggressive lymphomas (2) first described in 1928 by Maurice N.

Richter (3) who reported a case of a 46-year-old man with diffuse lymphadenopathy, massive organomegaly and a rapidly fatal clinical course as seen in untreated diffuse large B-cell lymphoma (DLBCL). Patients with Richter transformation (RT) typically present with constitutional symptoms (lost of weight, fever), rapidly enlarging lymph nodes, spleen or liver and increased lactate dehydrogenase (LDH) activity with histological features of DLBCL that are formally required to make a diagnosis of RT (4). The current estimated rate of Richter transformation in CLL is approximately 2-8% (4, 5). Although the most common type of histological transformation of CLL is to a high-grade B-non-Hodgkin lymphoma (NHL), other types of lymphomas have also been described, including Hodgkin lymphoma (6), small noncleaved cell lymphoma (7), lymphoblastic lymphoma (8), hairy cell leukaemia (9), and high-grade T-cell NHL (10, 11). Transformation of CLL/SLL to Hodgkin lymphoma, called "Hodgkin variant of Richter transformation (HLvariantRT) occurs very rarely (0.5% of patients with CLL/SLL) constituting 15% of RT. (6, 12-14) Although rare, it is considered one of the commonest second malignancies in patients with a known CLL. Increased risk of developing Hodgkin lymphoma among CLL patients when compared with the general population, with an observed-to-expected ratio of 7.69 was reported by Travis et al. (15).

Patients with CLL have also an increased risk (20%) of second malignancy compared to general population (15, 16). Significantly increased risks were observed for Kaposi sarcoma, malignant melanoma and cancers of the larynx and the lung (16). Presentation of second malignancy in patients with CLL may mimic RT symptoms causing delay in correct diagnosis, thus decreasing a chance of early intervention. Here we describe diagnostic and therapeutic difficulties in a 59-year old patient with CLL, who almost simultaneously developed non small cell lung cancer and Hodgkin variant of Richter syndrome two years after the diagnosis of CLL.

CASE REPORT

A 59-year old patient with a history of smoking, arterial hypertension, ischaemic heart disease and numerous ischaemic foci in the brain was referred in September 2005 to the haematology department because of leucocytosis combined with night sweats and general asthenia. Physical examination revealed generalised enlargement of peripheral lymph nodes (approx. 2 cm), mainly cervical and axillary without enlargement of the spleen and liver. Blood cell count showed leucocytosis (85 x 109/l) composed mainly of mature lymphocytes, anaemia (Hb approx. 10 g/dl) and thrombocytopenia (98 x 109/l). Imunophenotyping of lymphocytes was consistent (CD5(+) CD19(+)) with diagnosis of B-cell chronic lymphocytic leukaemia. The patient was started on chlorambucil, and achieved after 12 months a partial remission (reduction of leucocytosis and lymphocytosis to 16.6 and to 14.9 x 109/l, respectively, increase of Hb and platelets up to 13.3 g/dl and to 123 x 109/l, respectively) with resolution of systemic symptoms.

In February 2007 on physical examination, the patient was found an oedema of the left lower extremity, followed few days later by diarrhoea and fever of up to 39°C with shivers. The patient was admitted to the department for internal medicine. His WBC was stable (14.82 x 109/l, lymphocytosis 6.84 x 109/l) and haemoglobin and platelets were within normal range. Chest X-ray revealed a round lesion of approx. 15 mm in the right apex of the lung and a polycyclic right hilum of the lung. Radiographic evaluation including comparison with prior films suggested that the lesion in the apex of the right lung might be related to a putative past tuberculosis, whereas a widening of pulmonary hilum to the primary disease. Doppler test of deep veins in the left lower extremity indicated thrombosis in the sagittal vein, 1/2 of the distal femoral vein and popliteal veins. Following an antithrombotic therapy and administration of antibiotics, oedema of the left lower extremity disappeared with concomitant improvement of the patient's general condition. Chlorambucil and prednisone were re-introduced. The patient received two subsequent cycles and his general condition remained stable.

In April 2007 the patient reported numbness of the right upper extremity, pain of the right shoulder, itching, fever and dyspnoea leading to admission to the Department for Lung Diseases. Computed tomography of the chest and the abdominal cavity revealed bilateral pulmonary embolism and a concomitant lesion in the 2nd segment of the right lung (57 x 37 mm, fig. 1), with a rib destruction at that level and numerous enlarged lymph node groups – mediastinal, hilar, retroperitoneal and iliac.

Examination of a thin needle biopsy showed cells consistent with non-small cell cancer (upper sulcus

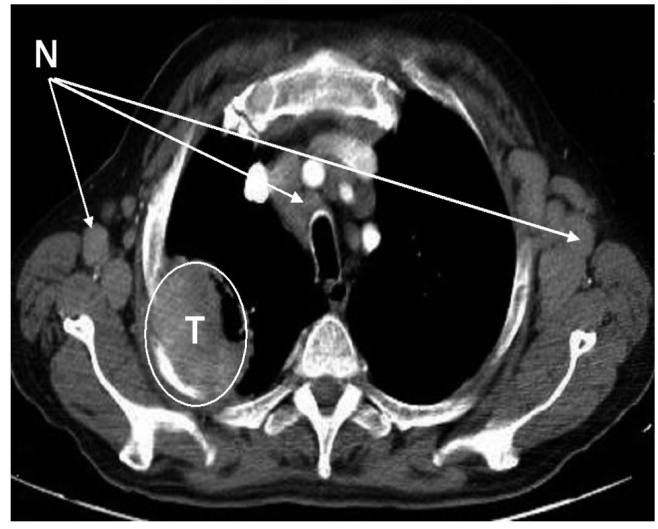

Fig. 1. Computed tomography scan of the 2nd segment of the right lung with a tumour (T) and associated rib destruction with enlargement of adjacent lymph nodes (N) in a CLL patient with Hodgkin variant of Richter transformation and concomitant lung cancer.

tumour). Mediastinoscopy was performed to investigate infiltration of enlarged mediastinal lymph nodes with lung cancer cells. The histopathological examination unexpectedly revealed Hodgkin lymphoma, type mixed cellularity (LCA(-), CD30(+), CD15 focal(+), CD20(-), CD3(-), CD23(-), consistent with Richter transformation of CLL. To alleviate clinical symptoms especially drenching sweats and fever not responding to antibiotics, ABVD chemotherapy was started. Clinical improvement was achieved confirmed by subsequent CT showing partial regression of enlarged lymph nodes, however, with concomitant progression of the lung tumour. Palliative radiotherapy was planned, unfortunately the patient died 6 months after diagnosis of the lung cancer and Richter transformation because of a massive pneumonia.

DISCUSSION

Our case indicates that new symptoms occurring during the course of CLL require careful differential diagnosis – they may indicate the progression of the disease but also the presence of second malignancy. Thus it stresses the need of histopathologic verification of all new, especially atypical lesions in such patients. In our patient the first symptom suggesting the presence of secondary malignancy was venous thrombosis, which is a well known sign of developing malignancy. The chest X-ray lesion in the right apex of the lung originally assumed as related to precedent tuberculosis was most likely the first sign of lung cancer. The histological evaluation of that lesion unfortunately was delayed that precluded any radical surgery. The right shoulder pain characteristic for Pancoast tumours that guided the right diagnosis occurred 3 months later. It was unfortunate since the prognosis of patients with CLL and solid tumour usually depends on the latter one, therefore prompt diagnosis of solid tumour is essential and such patients should not be *a priori* excluded from treatment if such is available.

Diagnosis of Hodgkin lymphoma during the work-up for lung cancer in our case was surprising. Resolution of systemic symptoms after ABVD chemotherapy suggests their relation rather to HL than to lung cancer. The development of HL in patients with CLL is considered as a variant of RT. It can occur any time during the course of the disease- the median time is being reported 31 (15), 45 (12) or about 100 (17) months after diagnosis of CLL. It is not related to the initial staging or clinical aggressiveness of CLL (12, 17). Bockorny recently (5) identified in the literature 86 such patients with HL variant of RT. The median interval between the diagnosis of CLL/SLL and subsequent development of Hodgkin lymphoma was 4.3 years (range, 0-26) and included nine patients who presented with simultaneous diagnosis of CLL and Hodgkin lymphoma. Most of the patients present, as our case did, with B symptomatology (86%) and rapidly progressive lymphadenopathy (71%) (6). All pathological subtypes of HL were described in patients with HL variant of RT (17, 18), but the most common was mixed cellularity as in our case. (10) The pathophysiology of this complication is not clear, even there is no certainty that HL derives from a CLL clone (2, 18, 19). Two types of Hodgkin transformation in CLL/SLL have been postulated in the existing literature. The type 1 transformation is consistent with the histological picture of RS cells scattered on a background of CLL cells (13, 20). Based on histological and immunophenotypic findings it is believed that RS cells represent histologically transformed CLL cells, especially in view of the fact that RS cells express B-cell markers and belong to the B-cell lineage. It has been hypothesized that B-CLL and HL-like cells derive from a shared germinal center B-cell precursor (21). In contrast, in type 2 transformation RS cells lay in a typical polymorphous, inflammatory background separately from the CLL cells (19, 22, 23). This led to the conclusion that RS cell origin is different from the origin of CLL cells. This theory is corroborated by reports of two cases where RS cells were found not be related to CLL clone (24, 25). Interestingly they contained Epstein-Barr virus (EBV) (26). This observation advocates for a role of EBV in the clonal expansion of an EBV-harbouring B cells, as suggested earlier by others (26, 27).

There are also some suggestions that Hodgkin's transformation of CLL may be more frequent after treatment with nucleoside analogues (5, 13, 17, 26, 27), but this has not been proven yet (2). Our case also does not support this notion since the patient did not receive any purine analogues. The prognosis in HL variant of RT is rather poor. The mean survival duration in report by Bockorny et al was approximately 1.7 years, a little longer than 2-3 months in classic RT (6, 12). Few patients, however, can achieve remission lasting for years after conventional chemotherapy (6, 28).

An increased incidence of lung cancer in patients with CLL has been observed for a long time. Although almost 2-3% of patients with CLL have been reported to die of lung cancer, 85% of these patients have been smokers, which makes understanding the relationship between CLL and lung cancer difficult (29). The predisposition of patients with CLL to the development of solid tumours is well known but the reasons of it are not clear (15, 30). It is speculated that it may be related to the immune defects associated with the disease itself. The lack of co-stimulatory molecules on CLL cells, along with the production of soluble cytokines that reduce T-cell function at least in part provides some explanation (31). Additionally the therapy given to CLL patients such as purine analogues may contribute to this phenomenon. However, there is no evidence to support that notion (16).

The other hypothetical explanation is the acquisition of shared genetic abnormality by CLL and solid tumour cells, in our case lung cancer cells. One of the candidate aberrations are structural abnormalities of chromosome 11. Patients with CLL with deletion 11q23 appear to be more prone to develop RT, probably because this region is considered to harbour genes, such as

the nerve cell adhesion molecule gene, that may play a role in the transformation (14). Locus 11q23.2 contains also the tumour suppressor gene TSLC1/IGSF4 inactivated by promoter methylation in various cancers, including about 40% of primary NSCLC tumours (32) especially in heavy smokers (33). The other candidate aberration could be trisomy 12 associated with high rates of CLL proliferation and disease progression (14, 34). In 1986 Liang et at al. showed a possible relationship between trisomy 12 and oncogene activation of the KRAS (a member of the RAS proto-oncogene family) localized on chromosome 12 (35). KRAS was found to be activated in some lung cancers by point mutations in 15-20% of all NSCLCs apart from SCLCs, especially adenocarcinomas (20-30%) and associated with smoking (36). The prospective molecular analysis of CLL and lung cancer cells would be the only way to test the above hypothesis. Regardless it is true, better understanding of molecular mechanism responsible for CLL progression and solid tumour development may help to identify earlier patients with high risk of both complications.

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received/otrzymano: 20.06.2012
accepted/zaakceptowano: 18.07.2012

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