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Case report/Kazuistyka

Richter's Syndrome manifested as diffuse large B-cell lymphoma of the mandible with lytic lesions and hypercalcemic crisis

Zespół Richtera objawiający się jako chłoniak rozlany żuchwy z dużych komórek B ze zmianami litycznymi i przełomem hiperkalcemicznym

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ABSTRACT

Richter's Syndrome (RS) is a transformation from chronic lymphocytic leukemia (CLL) into more aggressive lymphoma. RS occurs in about 5% of patients with CLL and its clinical outcome is poor. Extranodal involvements of RS may be present in up to 40% of patients and central nervous system manifestation was found to be the most common. Mandibular localization of RS has not been reported so far. There is no established standard treatment for RS. The improvement of survival in RS patients is achievable with intensive anti-lymphoma chemotherapy and subsequent allogeneic stem cell transplantation (alloHSCT) performed in complete remission. Herein we report a female with RS of the right mandible and hypercalcemia was its first clinical manifestation.

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Introduction

Richter's Syndrome (RS) known as Richter's transformation (RT) remains a rare complication of chronic lymphocytic leukemia (CLL) of any stage [1]. RS occurs in 5% of patients with CLL and its clinical outcome is poor with a median overall survival of about 8 months [2]. Extranodal involvements of RS may be present in up to 40% of patients and central nervous system manifestation was found to be the most common in a large study cohort. Bone localization remains extremely rare and RS of the mandible has not been reported so far. The clinical outcome is poor with a median overall survival of 5 months from the time of RS diagnosis [3]. Herein we report a female with a 3-year history of CLL who developed RS initially manifested as lytic lesion in the right mandible with hypercalcemic crisis.

Case report

A 45-year-old previously healthy female was admitted to our Department in January 2009 with a suspicion of chronic lymphocytic leukemia (CLL). She complained of protracted respiratory tract infection. On admission physical examination revealed the enlargement of cervical, axillar and inguinal lymph nodes. The abdominal ultrasound examination revealed hepatosplenomegaly and enlarged para-aortic lymph nodes. White blood cell (WBC) count was 21×10^9/L with an increased lymphocyte count (13.25×10^9/L). Hemoglobin (Hgb) concentration and platelet (PLT) count were normal. Biochemistry disclosed elevated serum lactate dehydrogenase (LDH = 253 IU/L; normal range: 91–180 IU/L) and β_2-microglobulin (β2 M = 8.59 mg/L; normal range: 1.5–3.0 mg/L). The bone marrow was infiltrated by small lymphocytes in 90%. The immunophenotyping of peripheral blood lymphocytes by flow cytometry was consistent with a diagnosis of CLL. The expression of CD38 and ZAP70 on lymphocytes was strongly positive. Fluorescence *in situ* hybridization (FISH) revealed deletion of 11q chromosome, no other abnormalities were detected. Disease stage was established to be II according to Rai. Nine cycles of CC regimen (Cyclophosphamide, Cladribine) were introduced as first line therapy. Patient's lymphocyte count returned to normal, she resolved peripheral lymphadenopathy but the enlarged lymph nodes were still present in her abdomen. Due to this finding she was started R-CHOP regimen (Rituximab, Cyclophosphamide, Adriamycin, Vincristine, Prednisone) with no response after 7 cycles. The suspicion of Richter's transformation prompted abdominal lymph node biopsy. The histopathologic examination was consistent with primary diagnosis of CLL. Patient was proceeded to subsequent lines of chemotherapy including: R-ESHAP (Rituximab, Etoposide, Cisplatin, Cytarabine and Methylprednisolone) and FMD (Fludarabine, Mitoxantrone, Dexamethasone) followed by palliative radiotherapy (30 Grey in 10 fractions on upper-mesentery lymph nodes). She achieved only minor decrease of tumor mass. Finally, she received RB regimen (Rituximab Benadmustine) but the treatment was complicated by Varicella Zoster Virus (VZV) infection. Subsequent cycles of chemotherapy were postponed. A few weeks later she was urgently admitted to our Department due to worsening of overall condition with marked confusion. There was recent history of tooth extraction. Physical examination revealed swelling of the right side of the face with unilateral gum infiltration. Blood counts were following: WBC count: 9.2×10^9/L with 37% of lymphoid cells in differential, Hgb concentration: 12.9 g/dl and PLT count: 18×10^9/L. Bone marrow biopsy showed 100% infiltration with lymphoid cells and immunophenotyping was typical for CLL. There were increased serum calcium (4.43 mmol/L; normal range: 2.10–2.55 mmol/L) and creatinine (225 μmol/L; normal range: 37–96 μmol/L) levels on biochemistry. The X-ray skeletal survey showed destruction of the right jaw with large lytic lesion and disseminated lytic lesions in scull, right humerus, scapula and ribs (Fig. 1). She developed diplopia and ptosis on the right. Magnetic Resonance Imaging (MRI) of the head revealed pathological infiltration of intracranial caves, bones and right carotid artery (Fig. 2). Histological examination of the biopsied gum was consistent with the diagnosis of DLBCL. She was started an intensive treatment for hypercalcemic crisis and CHOP treatment was introduced as a salvage regimen. The chemotherapy resulted in transitional improvement of overall condition but the symptoms of hypercalcemia recurred with subsequent fatal outcome despite intensive supportive care. The autopsy showed lymphoid infiltrations present in lymph nodes, bone marrow, spleen, pituitary gland, stomach, and kidneys.

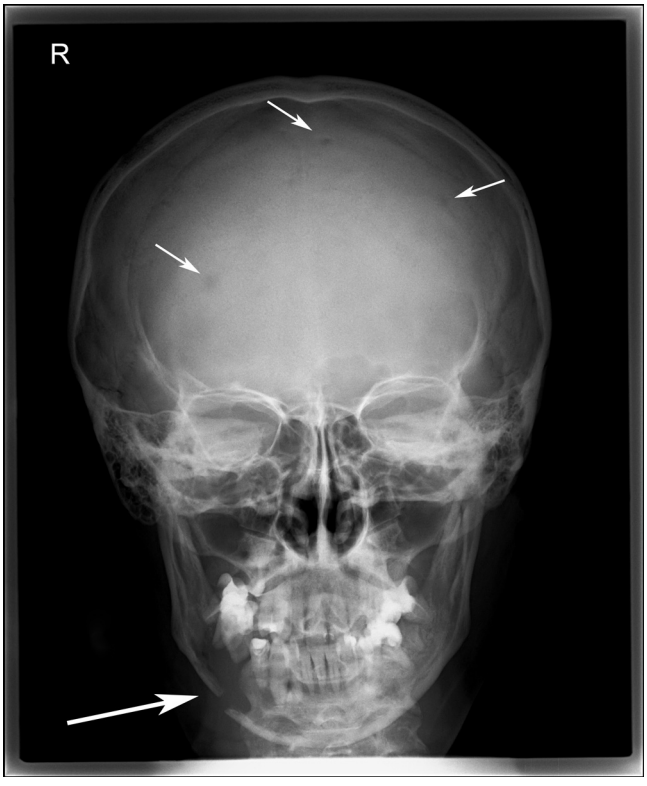

Fig. 1 – Skull X-ray. Osteolytic lesions seen in the bones of the skull. The longer arrow shows the pathological fracture of the right mandible, the shorter arrows show osteolytic lesions in skull)

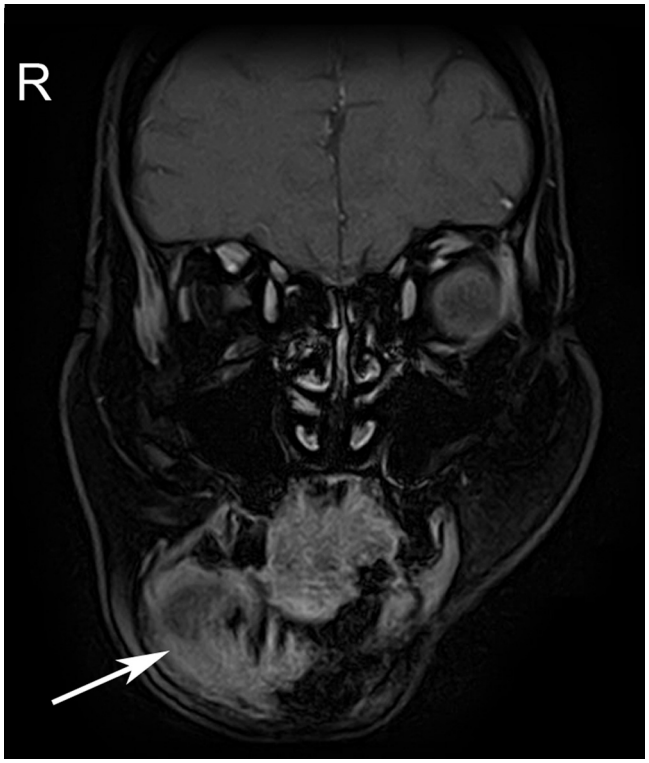

Fig. 2 – MRI scan of the head. Lymphoma infiltration of the mandible

Discussion

Richter's Syndrome remains a rare complication of CLL or SLL. Pathogenesis of RS remains unknown. It was postulated that transformation into aggressive lymphoma may be triggered by viral infection, especially EBV [1]. RT is manifested predominantly as diffuse large B-cell lymphoma (DLBCL), but presentations as Hodgkin lymphoma [4], lymphoblastic lymphoma [5] or hairy cell leukemia [6] were also reported. The extranodal manifestations in testis, central nervous system, skin or gastrointestinal tract were found to be the most common [3, 7–10]. To our best knowledge a patient with mandibular localization of RS has not been described in the literature so far. However, there are single cases of DLBCL localized in the mandible [11, 12]. It was demonstrated that RS may occur at both early and late phases of CLL and prompt diagnosis is crucial for clinical outcome [1, 13]. Hypercalcemia as the first manifestation of RS has been rarely reported so far [3, 14, 15]. All patients presented with hypercalcemia-associated RS had prior CLL and osteopenia with lytic lesions were found in X-ray survey. Two mechanisms of hypercalcemia were postulated. First it may results from an increased bone resorption which is due to secretion of osteoclast-stimulating factors by tumor cells. In addition an overproduction of interleukin IL-6 and tumor necrosis factor TNF-α seems to play a role in the development of hypercalcemia in single cases. Despite initial response to therapy with bone resorption inhibitors, the outcome was eventually fatal [14]. The same was also observed in our patient. Other study demonstrated that patients with hypercalcemia-associated DLBCL had shorter survival if compared to those with normal serum calcium level [16]. Several factors may predict the development of RS and they differ from those for CLL progression. A multivariate analysis including biological and clinical variables identified lymph node size $\geq$3 cm and the lack of deletion 13q14 as predictors of Richter's transformation [13]. It was also demonstrated that some genetic abnormalities were crucial for the development of RS and they had higher complexity and heterogeneity if compared to CLL. A detailed molecular characterization of 86 patients with RS has found that TP53 disruption and c-MYC rearrangements were the most common genetic alterations. Moreover, the absence of TP53 disruption was associated with an improved survival. This study revealed three predictors of RS survival and they were following: 1) TP53 status, 2) response to treatment and 3) ECOG performance [17]. Disease outcome in terms of clinical course and response to therapy was variable. There is no established standard treatment for RS. In a large study including 352 patients with probable or proven RS, an overall response was 39% and there was no difference between chemotherapy and chemoimmunotherapy. Most common therapeutic schema included purine analog-based therapy, Hyper-CVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone) or CHOP+/− anti-CD20 monoclonal antibody. It was also demonstrated that allogeneic hematopoietic stem cell transplantation (alloHSCT) used as remission consolidation may prolong survival in this patient cohort [2]. In summary, bone damage by lymphoma cells resulting in resistant hypercalcemia may be the first manifestation of RS. The prognosis remains fatal despite aggressive chemotherapy. Based on current experience the improvement of survival in RS patients is achievable with intensive anti-lymphoma regimens and subsequent alloHSCT performed in complete remission [2].

Authors' contributions/Wkład autorów

KWP – study design, data collection and interpretation, manuscript preparation, literature search. GH – study design, data interpretation, manuscript preparation. JDS – study design. KW, AF – data collection. GH – data interpretation, manuscript preparation. SKK – manuscript preparation.

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Conflict of interest/Konflikt interesu

None declared.

Ethics/Etyka

The work described in this article have been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

When submitting article with own research on people/animals, the research were conducted according to the Good Clinical Practice guidelines, all patients agreed in writing to participation and these researches were accepted by local Bioethics Committee.

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