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Case report ■

Extensive Bone Marrow Involvement in Hodgkin Lymphoma Patient

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SUMMARY

Bone marrow involvement is rare in patients with Hodgkin lymphoma (HL). Its incidence varies with respect to risk factors from 4% to 14%. Low risk patients do not need trephine biopsy according to some research. In the era of positron emission tomography/computed tomography (PET/CT) staging prior to therapy, the role of trephine biopsy as a part of staging procedures becomes debatable. Many institutions worldwide created their own guidelines in the application of trephine biopsy in staging of the (HL) patients. Our institution prefers performing trephine biopsy in all risk group patients, except those who underwent PET/CT staging before therapy and if no active bone sites were found. Most of our patients are staged using multislice computed tomography (MSCT) and we perform PET/CT in the follow up after completing the induction protocol. That is why we propose the trephine biopsy to the most of our patients. A Greek group of authors have derived a clinical prediction rule for the possibility of the bone marrow involvement, which is named the Z score (Zs), and if it is ≥10, patients are at high risk for bone marrow involvement.

We present a case of a neglected, advanced (HL) patient, with the defined high risk for bone marrow involvement (Zs=25). He was clinically suspected to have affected bone marrow, which was later histologically confirmed. Unilateral trephine biopsy was performed.

Key words: **Hodgkin lymphoma, bone marrow involvement, HRS cells, trephine biopsy**

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INTRODUCTION

Bone marrow involvement (BMI) is rare in patients with Hodgkin lymphoma (HL). Its incidence varies between 4% and 14% in the series reported during the past 20 years (1-3). According to the Ann Arbor staging criteria for HL, a bone marrow biopsy (BMB) is recommended for patients with any of the following: elevated serum alkaline phosphatase, stage III/IV disease, any unexplained cytopenia or radiographic/scintigraphic evidence of osseus involvement (4). The updated criteria from Cotswolds meeting in 1988 established the recommendations for BMB in patients with clinical stage II and adverse features (5).

Despite those formal recommendations many physicians perform biopsy in all patients. Our institution stands in the same position. We perform mostly unilateral BMB because it is a painful and shocking procedure. However, we double-check the marrow tissue by using May-Grunwald-Giemsa (MGG) stain for imprint preparations and the pathologists perform immunohistochemical examination as a mandatory option.

This case report presents a patient with advanced, neglected HL in clinical stage IV B, with extensive BMI.

CASE REPORT

A 55-year old male was admitted to our clinic with a generalized lymphadenopathy, cachexia, and pronounced B symptoms (night sweats, extreme fatigue, weight loss, constant fever). He was diagnosed with mixed cellularity type of classic HL (cHL) almost two years prior to hospitalization but refused to be treated.

During lymphoma-staging procedures, MSCT of the neck and mediastinum showed lymph node conglomerates approximately (10.3 X 9.3 cm in diameter) on the left side of the neck which extended from the upper parts of the neck to infraclavicular region (Bulky volume mass). Bilateral pleural effusions occurred in the mediastinum with hilar adenopathy on the right side and solid pulmonary infiltrates (3.8 cm in diameter) in the right lobe. MSCT of the abdomen and pelvis showed splenomegaly (spleen IP diameter 13.2 cm) with retroperitoneal lymphadenopathy of approximately 3.6 cm with ascites, and inguinal both sided lymphadenopathy. The profound anemia was found in the blood count with Hb 53 g/L, Hct 18%, RBC 2.18 X 10^9/L, WBC 3.3 X 10^9/L, Neu 1.6 X 10^9/L, Ly 1.0 X 10^9/L, PLT 98 X 10^9/L. Erythrocyte sedimentation rate was 110. Biochemistry findings: glucose 3.5 mmol/ L, urea 4.1 mmol/L, creatinine 49.7 μmol/L, uric acid 90.2 μmol/L, total bilirubin 11.1 μmol/L, direct bilirubin 4.5 μmol/L, total proteins 63.7 g/L, albumine 15.6 g/L (low), AST 30.7 U/L, ALT 11.3 U/L, ALP 272 U/L (high), LDH 952.8 U/L (high), CRP 155.1 mg/L (high), GGT 36.3 U/L, Fe 2.5 μmol/L (low), Ca 1.80 mmol/L (low), K 4.2 mmol/L, Na 130 mmol/L, Cl 98 mmol/L. Plasma immunoglobulins: IgG 29.20 g/L (high), IgA 4.04 g/L, IgM 0.42 g/L, β2 microglobuline 15 mg/L (high), no M component was found in plasma. Coombs test was positive with direct antiglobuline test (DAT++). He was HIV and HBsAg negative, but HCV positive. The heart ejection fraction (EF) was 56%. Unilateral BMB was performed. The imprint MGG staining preparation showed "owl eyed" cells diffusely dispersed in hypercellular marrow (Figures 1-E, F). Hematoxyllin-eosin staining showed hypercellular marrow over 90%. Elements of regular hematopoiesis were almost completely suppressed by neoplastic infiltrates which were composed of numerous multinucleated or cells with bilobed nuclei marked as Hodgkin/Reed-Sternberg (HRS) cells, with a prominent inclusion-like nucleoli and abundant cytoplasm (Figure 1-A). Reticular fibrosis was pronounced with foci of collagen fibrosis. Immunohistochemical profile: strong CD30 expression of HRS cells (Figure 1-B), strong Pax-5 (BSAP) positivity (Figure 1-C) and intense labeling with CD15 of HRS cells (Figure 1-D).

After the completion of staging procedures the patient was staged as cHL in clinical stage IV B, b, V+ (Bulky disease). The International Prognostic Score (IPS) for HL was 4 (high risk HL). Induction treatment included ABVD (doxorubicin, bleomycine, vinblastine and dacarbazine) regimen. Our patient received four cycles of ABVD regimen and partial remission was obtained. The therapies are still ongoing.

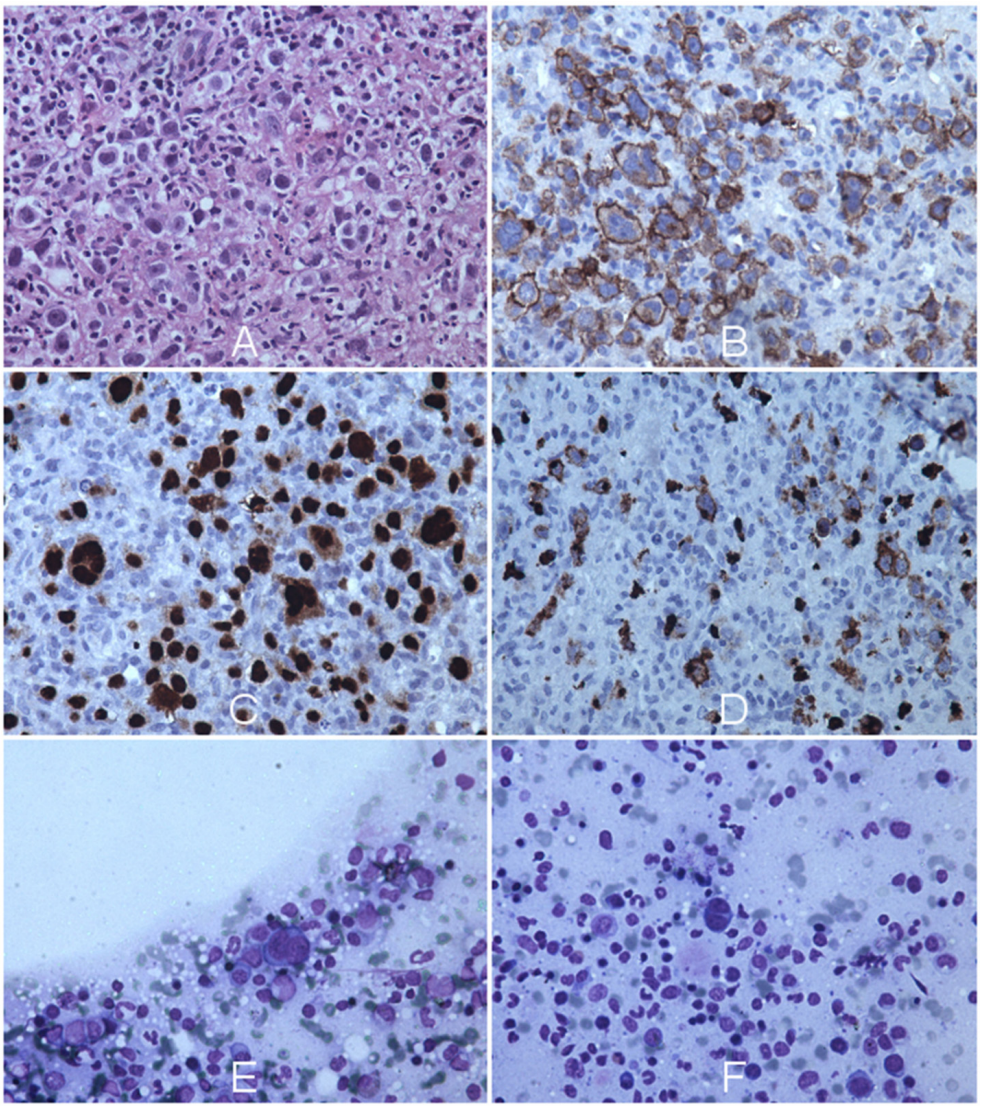

Figure 1. *Extensive bone marrow infiltration with Hodgkin/Reed-Sternberg (HRS) cells. (A-D) Representative staining of biopsy specimens: (A) H&E stain; note the HRS cells, multinucleated or with bilobed nuclei, prominent inclusion-like nucleoli and abundant cytoplasm. (B) Strong CD30 expression in HRS cells. (C) Neoplastic cells showing strong positivity to Pax5 (BSAP). (D) Intense labeling of HRS cells by CD15 antibody. (E, F) Imprint cytology smear demonstrating the presence of HRS cells.*

DISCUSSION

As mentioned in introduction, BMB in early stage of HL might be avoided according to Ann Arbor and Cotswold criteria, but there is no consensus between experts regarding its use in the initial staging of HL. Various clinical and laboratory factors have been encountered to predict BMI, including B symptoms, stage III/IV, peripheral cytopenias, elevated serum lactate dehydrogenase (LDH), splenic involvement, and mixed cellularity/lymphocytic depletion histology (1-3, 6). Trephine biopsy is a painful and invasive procedure, and we have found in the literature that patients with HL could be stratified in order to perform or to avoid this procedure. Patients with low risk for BMI could be spared from such procedure. Conversely, patients with relatively high risk of BMI might benefit from bilateral trephine biopsy, because the probability of demonstrating BMI can be increased by 16% to 33% if bilateral biopsy is performed (2, 7, 8). Vassilakopoulos et al. published a clinical prediction rule for BMI in HL based on 826 patients and validated it in 654 additional patients (9). They used six simple clinical features of HL: B symptoms-X1, stage III/IV prior to BMB-X2, anemia-X3, leukocytes fewer than 6 x 10^9/L-X4, age ≥35 years-X5 and iliac/inguinal involvement-X6. Each factor was graded as 1 point if present or 0 if absent. A simplified score Zs= 8X1+6X2+5X3+5X4+3X5+3X6-8 was assigned for each patient. The aforementioned group determined the three risk groups of patients: 0.44% of patients had a low risk for BMI - 0.3%, Zs<0, standard risk was found in 37% of patients, with Zs 0-9 and their risk for BMI was 4.2%, and

finally a high risk group including 20% of all patients, with Zs≥10 had 25.5% risk for BMI. Patients with low risk (stage IA/IIA without anemia and leukopenia; stage IA/IIA, younger than 35 years, with either anemia or leukopenia but no inguinal/iliac involvement; and stage IIIA/IVA without any of these 4 risk factors) do not need BMB. Patients with standard risk should be staged with unilateral biopsy, but patients with high risk may benefit from bilateral biopsy (9). As for this scoring system, our patient was absolutely in high risk group population (Zs was 25).

BMI alone does not define a special high-risk group in which a different treatment approach is indicated (10). Prognosis of the patients with BMI is not worse than the prognosis of other advanced-stage HL patients. Currently, reports are that the use of routine BMB in the era of PET/CT in staged treatment-naive HL patients has little or no therapeutic consequences (11).

CONCLUSION

Despite the current reports of withdrawing BMB for the patients with negative PET/CT prior to starting the induction therapy, we do not perform such action in most of the cases, due to the unavailability of the method in our country prior to therapy. BMB is still the essential part of the staging procedure in our institution. The aim of this article was to present the usefulness of Zs in clinical practice and to demonstrate rarely seen images of extensive BMI in patient with highly advanced HL.

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EKSTENZIVNO ZAHVATANJE KOŠTANE SRŽI KOD BOLESNIKA SA HOČKINOVIM LIMFOMOM

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Sažetak

Infiltracija koštane srži kod bolesnika sa Hočkinovim limfomom (HL) je retka. Incidencija varira u zavisnosti od faktora rizika od 4% do 14%. Niskorizični bolesnici nemaju potrebe za biopsijom koštane srži, što pokazuju neka istraživanja. U eri PET/CT stadiranja pre primene terapije, potreba za biopsijom koštane srži, kao deo stadiranja HL, postaje diskutabilna. Mnoge ustanove u svetu imaju svoje sopstvene vodiče za biopsiju koštane srži u toku stadiranja HL. Naša ustanova ima mogućnosti da sprovodi biopsiju koštane srži bolesnicima svih rizičnih grupa, sem onih koji imaju urađen PET/CT pre početka uvodne terapije i ukoliko nisu detektovani aktivni koštani fokusi. Kod većine naših bolesnika stadijum bolesti se određuje primenom MSCT-a, dok PET/CT sprovodimo u praćenju terapijskog odgovora nakon završetka indukcionog protokola. Grčka grupa autora razvila je kliničku predikcijsku šemu za mogućnost infiltracije koštane srži, koju su nazvali Z skor (Zs), čija vrednost ≥10 ukazuje da bolesnici imaju visok rizik za infiltraciju koštane srži.

Prezentujemo slučaj bolesnika sa zapuštenim, uznapredovalim HL, sa definisanim visokim rizikom za infiltraciju koštane srži, Zs je bio 25. Kod bolesnika je postojala klinička sumnja na infiltraciju koštane srži koja je kasnije i patohistološki potvrđena. Primenjena je unilateralna biopsija.

Ključne reči: **Hočkinov limfom, infiltracija koštane srži, HRS ćelije, biopsija koštane srži**