Acta Clin Croat 2025; 64:650-653
doi: 10.20471/acc.2025.64.03.25

Case Report

AGGRESSIVE PRIMARY ADRENAL LYMPHOMA PRESENTING AS POORLY DIFFERENTIATED CARCINOMA: A CASE REPORT

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SUMMARY – Primary adrenal non-Hodgkin lymphoma (PAL) is an extremely rare extranodal lymphoma. Diffuse large B-cell lymphoma (DLBCL) is the most common PAL subtype with a high rate of bilateral involvement. We describe a unique clinical course in a patient with PAL initially misdiagnosed as poorly differentiated carcinoma. After four cycles of initial treatment with a protocol for disseminated carcinoma of unknown primary site, evaluation showed progression of the disease. Another biopsy of the adrenal gland was performed and showed aggressive non-Hodgkin lymphoma of DLBCL phenotype. After 8 cycles of R-CHOP therapy, the patient achieved complete remission which was confirmed by PET-CT scan, together with marked clinical improvement and withdrawal of signs of adrenal insufficiency which he developed during R-CHOP therapy. In conclusion, a diagnosis of PAL is frequently challenging due to its nonspecific clinical and radiological manifestations, and requires invasive procedures for pathologic examination. Inadequate biopsy sample can lead to misdiagnosis and exposure to inappropriate therapies since PAL is an extremely rare disease.

Keywords: *Adrenal gland neoplasms; Adrenal insufficiency; Non-Hodgkin lymphoma*

Introduction

Primary adrenal non-Hodgkin lymphoma (PAL) is an extremely rare extranodal lymphoma with only 100 cases described in medical literature[1]. Conversely, secondary involvement of adrenal glands is much more common and occurs in nearly 25% of patients with non-Hodgkin lymphomas[2]. Diffuse large B-cell lymphoma (DLBCL) is the most common PAL subtype with a high rate of bilateral involvement[3,4]. Diagnosis of PAL is frequently challenging due to its nonspecific clinical manifestations and requires invasive procedures for pathologic examination[5]. Here

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Received May 21, 2020, accepted September 29, 2020

we describe clinical presentation and a unique clinical course in our patient with PAL initially misdiagnosed as poorly differentiated carcinoma.

Case Report

This case report was approved by the institutional Ethics Committee and is in accordance with ethical standards laid down in the Declaration of Helsinki from 1964. The patient signed the informed consent form and his identity remains anonymized.

A 71-year-old male patient was diagnosed with bilateral adrenal hypertrophy in October 2017, after a period of abdominal disturbance and weight loss. Multislice computed tomography (MSCT) guided percutaneous biopsy of the left adrenal gland was performed and it showed the presence of poorly differentiated carcinoma, however, wide immunohistochemical panel could not be done because of small biopsy sample (Fig. 1A). Further diagnostics were performed, including MSCT scan of the thorax and bronchoscopy, which excluded existence of malignant pulmonary disease, and common tumor markers were negative. Treatment was started with a protocol for disseminated carcinoma of unknown primary site (GC protocol, a combination of gemcitabine and cisplatin). Follow up evaluation after four cycles showed progression of the disease (enlargement of the left adrenal gland from 56x18 to 62x23 mm and right adrenal gland

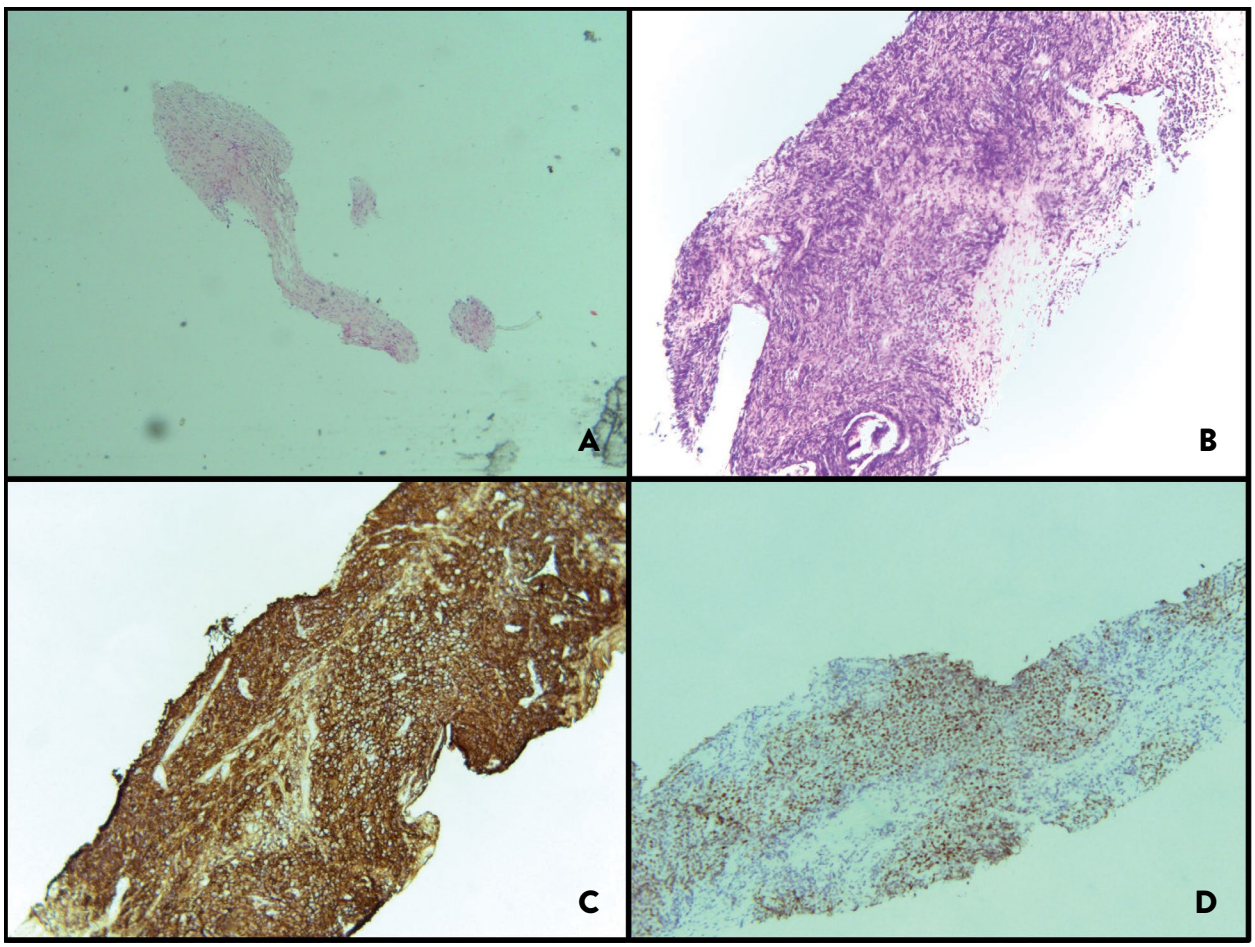

Fig. 1. Poorly differentiated carcinoma: (A) in inadequate biopsy sample; (B) diffuse large B-cell lymphoma of the right adrenal gland; (C) with expression of CD20; and (D) with expression of myc.

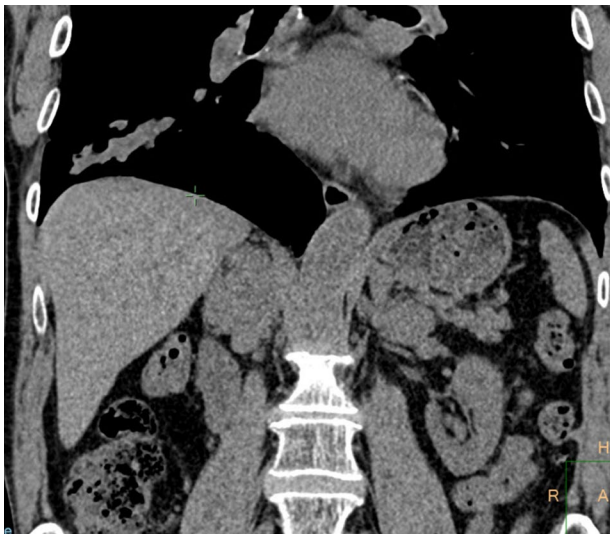

Fig. 2. Multislice computed tomography scan of adrenal non-Hodgkin lymphoma with bilateral involvement.

from 68x56 to 73x63 mm) (Fig. 2). This time, biopsy of the right adrenal gland was performed and the patient was diagnosed with aggressive non-Hodgkin lymphoma of DLBCL phenotype (non-GCB, Ki-67 >80%, myc/bcl-2 double expressor, rearrangement of myc excluded by fluorescence *in situ* hybridization) (Fig. 1B-D). There was no bone marrow involvement as judged from bone marrow biopsy, and nodal involvement was excluded with MSCT scans and physical examination. The patient had poor performance status (Eastern Cooperative Oncology Group 3) and high-intermediate International Prognostic Index risk (IPI 3). Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) was started in May 2018. After 4 cycles of R-CHOP therapy, the patient developed severe hyponatremia together with clinically manifest adrenal insufficiency despite adequately responding disease (partial remission on interim MSCT scan), and supplementary hydrocortisone was instituted. After 8 cycles of R-CHOP therapy, the patient achieved complete remission which was confirmed by positron emission tomography-computed tomography scan, together with marked clinical improvement and withdrawal of signs of adrenal insufficiency while remaining on glucocorticoid treatment. The patient remains in disease remission and is well now, 7 years after the end of treatment.

Discussion

Several interesting observations emerge from our case. In the case of PAL, adequate biopsy sample and experienced pathologist are of utmost importance to establish proper diagnosis on time. Image guided fine needle aspiration or biopsy must be regarded as the investigation of choice for early confirmation or exclusion of malignant diseases[6]. Inadequate biopsy sample can lead to misdiagnosis and exposure to inappropriate therapies since PAL is an extremely rare disease with non-specific clinical and radiological manifestations. Bilateral enlargement of adrenal glands can sometimes be seen in asymptomatic individuals on routine radiological imaging. Therefore, constitutional symptoms such as weight loss might raise suspicion of some rare adrenal malignancies, in this case PAL. Physicians should be aware that life-threatening consequences of adrenal insufficiency can develop late during treatment, even after achieving response of a chemo-sensitive disease, therefore, glucocorticoid replacement therapy might be necessary[7]. The prognosis of PAL is poor with median survival being around one year, which in general is worse than in other extranodal lymphomas[8]. The wide systemic spread of the disease, including central nervous system invasion that is reported in up to 50% of patients with adrenal lymphoma, is one of the factors that are associated with a poor prognosis[9]. Immunochemotherapy is still the cornerstone in the management of aggressive lymphomas. As presented in our case, classic R-CHOP regimen seems to be an effective and feasible therapeutic approach as the first-line option even in elderly patients with poor performance status.

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Sažetak

AGRESIVNI PRIMARNI LIMFOM NADBUBREŽNIH ŽLIJEZDA PREZENTIRAN KAO SLABO DIFERENCIRANI KARCINOM: PRIKAZ SLUČAJA

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Primarni ne-Hodgkinov limfom nadbubrežnih žlijezda (PAL) iznimno je rijetka vrsta ekstranodalnog limfoma. Difuzni B velikostanični ne-Hodgkinov limfom (DLBCL) je najčešći podtip PAL-a i u pravilu se prezentira bilateralnom infiltracijom. U ovom članku prikazujemo jedinstveni slučaj PAL-a koji je prethodno pogrešno interpretiran kao slabo diferencirani karcinom. Nakon početnog liječenja kemoterapijskim protokolom za liječenje diseminiranih karcinoma nepoznatog primarnog sijela kontrolna obrada ukazala je na progresiju bolesti. Ponovljenom biopsijom nadbubrežne žlijezde dijagnosticiran je agresivni limfom te se liječenje nastavilo s 8 ciklusa imunokemoterapije prema protokolu R-CHOP. Uz znatno kliničko poboljašanje nakon završetka liječenja PET/CT-om je potvrđena potpuna remisija bolesti, a nestali su i simptomi adrenalne insuficijencije koju je bolesnik razvio za vrijeme liječenja. Postavljanje dijagnoze PAL-a nerijetko je velik dijagnostički izazov zbog nespecifične kliničke i radiološke prezentacije, a invazivni zahvati nužni su za dobivanje uzorka za patohistološku analizu. Neadekvatni i mali biopsijski uzorci vrlo lako mogu dovesti do pogrešne interpretacije budući da se radi o iznimno rijetkoj bolesti.

Ključne riječi: *Novotvorine nadbubrežne žlijezde; Adrenalna insuficijencija; Ne-Hodgkinov limfom*