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Primary adrenal non Hodgkin lymphoma: Changing trends

To the Editor,

We found the case report on primary adrenal lymphoma (PAL) by Ezer et al. (2011 December, Turkish Journal of Gastroenterology) interesting (1). However, certain aspects of PAL, particularly pathology, adrenal function, and changing trends in management, are worth highlighting (Table 1).

Primary adrenal lymphoma's pathogenesis is multifactorial, with various mechanisms suggested, including 1) immune dysregulation (immune deficiency and autoimmunity, the most common); 2) originating from hematopoietic tissue resting within a single adrenal gland; 3) p53 and c-KIT gene mutation. The so-called "homing mechanism" (i.e., originating from hematopoietic tissue resting within one adrenal gland and gravitational migration to the contralateral side) may also partly explain the bilaterality common in this malignancy (2). The adrenal gland, like the thyroid, is normally devoid of lymphoid tissue; immune dysregulation predisposes to forming polyclonal lymphoid infiltrate (acquired mucosa associated lymphoid tissue) and subsequent clonal evolution into lymphoma, in which Epstein-Barr virus and JC polyoma virus play a role (3,4).

Background autoimmune adrenalitis and direct infiltration by neoplastic lymphoid cells are postulated to be the most common mechanisms of adrenal hypofunction observed in PAL patients. Considering that >90% of the adrenal gland needs to be destroyed before adrenal pathology becomes clinically apparent, increasing numbers of PAL patients are currently being diagnosed with preserved adrenal function (1). This, in combination with nonspecific clinical features and imaging characteristics, makes early diagnosis more challenging.

Diffuse large B-cell NHL (DLBCL) is the most common type of PAL reported till date, with only 5 of the non-B

Table 1. Primary adrenal non-Hodgkin lymphoma (PAL): brief review of literature from selected series of patients

Authors (ref.)	No. of Patients, Ethnicity	Adrenal Insufficiency	Clinical Parameters	Pathology€	Therapy≠	Outcome
Mojos et al. (4)	10 Taiwanese-6 Spanish-3 British-1	1/10	Advanced stage±	8 DLBCL, 1 PBL, 1 NKTCL, BCL-6 positive EBV positive	CT	Poor
Yun et al. (5)	14 Korean	ND¶	Advanced stage±	13-DLBCL 1-NKTCL	CT±RT (10/14); Surgery±CT (4/14)	Poor
Wang et al. (6)	55 (30 Japanese)	20/40 (tested)	Advanced stage±	B-NHL, rarely T-NHL	CT	Poor (24 cases autopsy diagnosis)
Kim et al. (7)	31 Korean	6/16 (tested)	10/31-stage$ I, 9/31-stage II, 12/31-stage IV, 21-low/intermediate IPI£, 10-high IPI	DLBCL (31/31)	CT	Favorable. Stage$ I/II; favorable than stage IV

¶, not documented; ±, Ann Arbor staging system; $, modified Luano staging system similar to that used for gastrointestinal lymphoma; £, modified International Prognostic Index scoring system; €, DLBCL-diffuse large B cell non-Hodgkin lymphoma
PBL: plasmablastic lymphoma, which was reported in a non-HIV patient; NKTCL: extranodal natural killer/T cell non-Hodgkin lymphoma; EBV: Epstein-Barr virus; ≠, CT, rituximab-based combined systemic chemotherapy; RT: postoperative radiotherapy to the adrenal bed; surgery, adrenalectomy

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cell phenotype (1 CD30 positive anaplastic large cell lymphoma and 3 T cell, 1 NK/T cell lymphoma of nasal type). Recent studies on primary adrenal DLBCL showed predominance of a nongerminal center B cell phenotype with increased expression of BCL-6 and MUM-1, which together confer poor prognosis in these patients (4,5).

Previous studies reported unfavorable outcomes of primary adrenal DLBCL; presently, no consensus exists for optimal management (5-7). Mojos et al. reported unfavorable outcomes among 10 PAL patients with BCL-6 gene rearrangements, despite preserved adrenal function (1/10 adrenal insufficiency) (4).Wang et al, in a review of 55 patients, found no correlation between adrenal hypofunction (20/40 tested) and tumor size (6). However, a recent study reported favorable therapeutic outcomes among 31 patients (6/16 with adrenal insufficiency) following rituximab-based chemotherapy when applying modified Lugano staging (similar to that used for gastrointestinal lymphoma) and modified International Prognostic Scoring (IPS) system (7). Bilateral adrenal involvement was considered as stage I (single site/extranodal) rather than Ann Arbor stage IV. The modified low/intermediate IPS category showed longer overall survival than the high-risk category, although progression-free survival did not differ between groups. Thus, a high index of suspicion, early diagnosis, and prompt therapy with a modified approach may offer some hope for these patients. The authors deserve congratulations for highlighting this rare entity and creating awareness among physicians.

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