Received: 16 September 2019 | Revised: 26 November 2019 | Accepted: 27 November 2019

DOI: 10.1002/jcla.23173

CASE REPORT

WILEY

Adrenal diffuse large B-cell lymphoma with high PD-L1 expression: Two case reports and literature review

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 81700182; Natural Science Foundation of Shanxi Province, Grant/Award Number: 201601D202094

Abstract

Background: Primary adrenal lymphoma (PAL) is an infrequent malignant disease and there is no consensus classification or specialized treatment for it. However, PAL has been observed to have worse prognosis compared with other extrarenal malignant lymphomas and diffuse large B-cell lymphoma presents as the most common subtype of PAL.

Methods: The current study reported two cases of adrenal diffuse large B-cell lymphoma with high PD-L1 expression and discussed the clinical significance of PD-L1 through literature review.

Key Results: The PD-L1 expression rate of the two cases was 90% and 80%, respectively, which was significantly higher than those reported in the literature.

Conclusion: PAL is a type of non-Hodgkin's lymphoma with low incidence and poor prognosis, and it is necessary to further explore the early use of immunological checkpoint inhibitors for patients with higher expression of PD-L1 and with rituximab-resistance.

KEYWORDS

adrenal lymphoma, diffuse large B-cell lymphoma, PD-L 1

1 | CASE REPORT

In case one, Hong XX, A 73-year-old female was admitted to another hospital due to the abdominal pain in the right lumbar region in October 2018. The abdominal ultrasonography showed hypoechoic nodule at both adrenal glands, which was about 48 × 18 mm and 32 × 15 mm, respectively. The blood routine revealed: WBC 2.90 × 10^9/L (normal range: 4-10 × 10^9/L), Hb 104 g/L (normal range: 110-150 g/L), and PLT 113 × 10^9/L (normal range: 100-300 × 10^9/L). The record of baseline adrenal function was missing. The biochemical profile revealed: LDH 241 U/L (normal range: 135-225 U/L) and albumin 33.5 g/L (normal range: 40-55 g/L). The test for Epstein-Barr virus DNA was negative. Positron emission tomography-computed tomography (PET-CT) showed the hyperplasia region of FDG metabolism at bilateral adrenal glands (SUV value = 32), right pleural (SUV = 20.7), and metastatic lymph nodes in the right hilum of the lung and porta hepatis. The adrenal pathology revealed: CD20(+), CD79a(+), MUM-1(+), CD3(−), C-myc(30%+), CD10(−), BCL-2(+), BCL-6(+), and Ki-67(50%+). The patient was finally diagnosed as bilateral adrenal diffuse large B-cell lymphoma (DLBCL) (IV group in Ann Arbor system stage and 3 points in IPI score). Then, R-CHOP regimen for two courses was administered since November 20, 2018, and R-EPOCH regimen for another two courses because of the abdominal ultrasonography showed hypoechoic nodule in the right adrenal gland had not decreased. After that, another PET-CT on May 30, 2019, showed that the hyperplasia region of FDG metabolism in

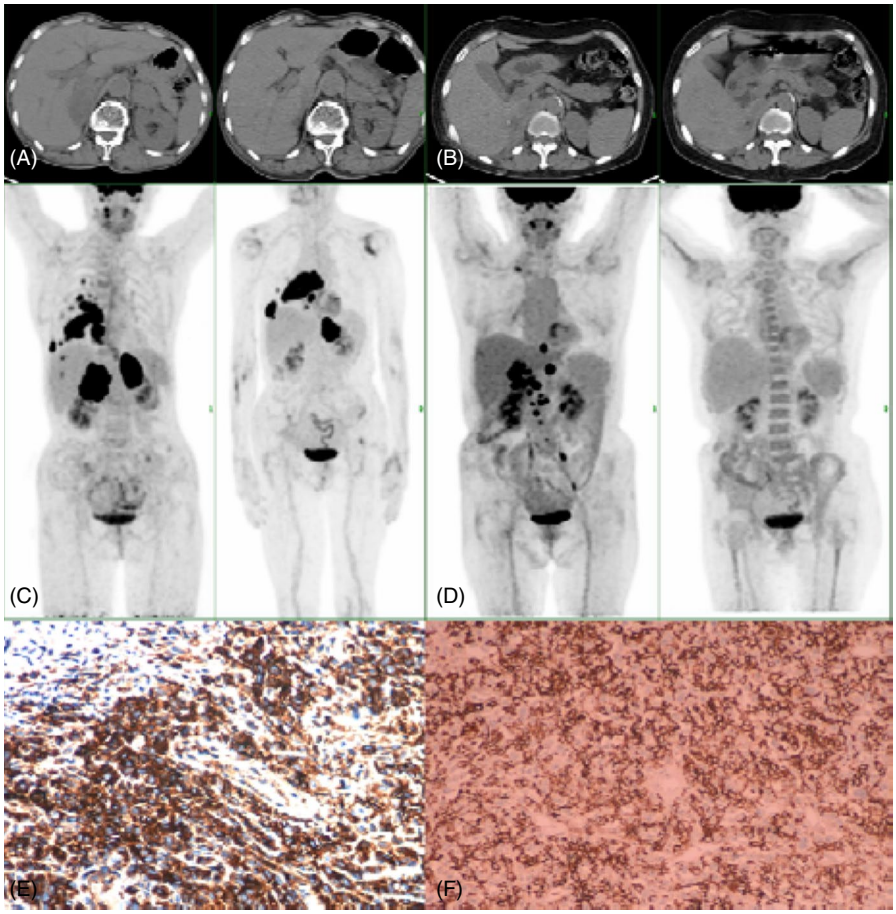

FIGURE 1 A, CT for case one before and after treatment. B, CT for case two before and after treatment. C, PET-CT for case one before and after treatment. D, PET-CT for case two before and after treatment. E, PD-L1 stain for case one (×400). F, PD-L1 stain for case two (×400)

the right adrenal gland as well as metastatic lymph nodes in the right hilum of the lung and porta hepatis had disappeared, while the others in the left adrenal gland and the lung still remained (Figure 1A,C). The regimens were then adjusted to R-GemOx regimen for two courses and RR-MINE regimen for one course. On July 10, 2019, this patient was admitted to our department for the first time and underwent supplementary pathological examination, which revealed: PDL1 (>90% malignant cells +) (Figure 1E). However, the patient and her family refused further treatment and the patient was discharged from our hospital.

In case two, Ni XX, a 64-year-old female, has been experiencing fatigue since October 2018 and her blood routine showed low WBC. In addition, the CT revealed a 10 × 10 cm size mass in the right adrenal gland. The patient was admitted to the department of urology in our hospital, where she received the right adrenal tumor resection surgery on October 9, 2018. The adrenal function showed: angiotensin II 62.989 pg/mL (normal range: 25-129 pg/mL), aldosterone (ALD) 153.675 pg/mL (normal range: 10-160 pg/mL), renin (PRA) 8.096 pg/mL (normal range: 4-24 pg/mL), and cortisol: 0 AM: 21.03 μg/dL, 8 AM:19.84 Ug/dL (normal range: 4.26-24.85 pg/mL), 16 PM:18.63 ug/dL (normal range: 2.7-17.3 pg/mL). The histological examination showed BCL-2(+), BCL-6(+), CD30(+), CD10(−), CD20(+), CD79a (+), CD3(−), and Ki-67 (70%+). The patient was first admitted to our department in early November 2018. The PET-CT showed hyperplasia region of FDG metabolism in lymph nodes of the right supraclavicular region, esophageal, right temporal region, hilar region, and retroperitoneal. The blood routine revealed WBC 2.50 × 10^9/L, Hb 123 g/L, and PLT 213 × 10^9/L. The biochemical profile revealed: LDH 161 U/L and albumin 42.5 g/L. The biochemical profile revealed LDH 161 U/L (normal range: 135-225 U/L) and albumin 42.5 g/L (normal range: 40-55 g/L). The test for Epstein-Barr virus DNA was negative. The patient was finally diagnosed as bilateral adrenal diffuse large B-cell lymphoma (IV group in Ann Arbor system stage and 3 points in IPI score). Then, CHOP regimen for one course since November 24, 2018, and R-EPOCH regimen for seven courses since December 7, 2018, was administered. The PET-CT on March 8, 2019, showed that the hyperplasia region of FDG metabolism had disappeared (Figure 1B,D). The supplementary pathological examination at July 29, 2019, revealed PDL1 (about 80% malignant Cells +) (Figure 1F). The test results suggested stable disease.

2 | DISCUSSION

Although there is currently no uniformed diagnostic criteria for primary adrenal lymphoma (PAL),[1] most scholars believe that PAL refers to the unilateral or bilateral adrenal lymphoma by histological examination and meets the following two criteria: (a) no previous lymphoma and (b) adrenal lymphoma should be dominate whether

other lymph nodes or other organs are involved or not. In this case report, the two patients had no previous history of lymphoma, and both of them were admitted to the hospital because of the adrenal mass, which basically met the PAL diagnostic criteria.

The incidence of PAL is rather low, and it is reported to be less than 1% of that in non-Hodgkin's lymphoma. Diffuse large B-cell lymphoma, accounting for 78% of all cases, is the most common type of PAL[2] with most of them being Bcl-6 rearrangement and non-germinal type, and bilateral lesions account for 50% to 70%.[3] Primary adrenal lymphoma usually occurs in the old, with an average age of 70 years. Male patients are more susceptible, and male/female ratio is 7:1.[4] The two cases reported in this report were elderly female including one with bilateral lesions and one with unilateral lesion, and both were non-germinal pathological type. Since the adrenal gland is concealed and the mass has no endocrine function, there is no obvious clinical symptoms of PAL until the tumor grows and compresses the surrounding tissues or organs, which makes it difficult for early diagnosis.[5] In this study, the two patients were both at stage IV at hospital admission. Therefore, a clear diagnosis at an early stage is crucial for improving the prognosis of such patients.

The pathogenesis of PAL is still unclear, and it is reported that the possible sources of PAL include undifferentiated pluripotent mesenchymal cells around the adrenal gland, hematopoietic cells of adrenal myeloid adipoma, and history of autoimmune diseases similar to other exodular lymphomas such as thyroid gland.[6] Another study discloses that the pathogenesis of PAL may be related to EB virus infection, p53, and c-kit gene mutation.[7] The two cases in our center presented with no history of autoimmune disease and serum Epstein-Barr virus test negative, while gene tests were not performed. Thus, further research is needed to explore the disease pathogenesis. The median survival of PAL was 13 months, which was significantly shorter compared with systemic DLBCL.[8] This could be due to the hidden manifestations, and most PAL cases are in the late stages at diagnosis. There are several prognostic markers for PAL such as IPI score, non-germinal, Bcl-6 rearrangement, old age, bulky disease, LDH higher than normal and involvement of other organs, which are also used in the systemic DLBCL.[9] Furthermore, bilateral adrenal involvement and adrenal insufficiency are the characteristic prognostic factors for PAL.[10] Adrenal insufficiency is found in 50% of PAL, and it presents no significant correlation with the size of the adrenal mass. The two cases in our study were both with poor prognosis, which was consistent with the literature.

Additionally, it is worth mentioning that the two cases both presented PD-L 1 positive, whose high expression is considered to correlate with poor prognosis in DLBCL patients. In a trial enrolling 1253 DLBCL patients, the expression rate of PD-L1–positive DLBCL cells was reported to be 11%.[11] And the GOELAMS075 study showed that patients with higher PD-L1 expression (above 1.52 ng/mL) had lower 3-year OS (76% vs 89%, $P < .001$) compared to patients with lower PD-L1 expression, and the expression of PD-L1 was significantly decreased with the remission of the disease.[12] It is also reported that higher expression of PD-L1 is more common in non-germinal and EBV-positive patients,[13] and the central nervous system DLBCL patients showed higher PD-L1 expression rate (58% vs 37%, $P < .001$) compared with the systemic DLBCL patients.[14] The PD-L1 expression rate of the two cases was 90% and 80%, respectively, which was significantly higher than those reported in the literature. However, due to the low disease incidence and limited cases, whether adrenal DLBCL is prone to higher PD-L1 expression rate or whether higher PD-L1 expression is a factor affecting its prognosis still needs further confirmation in large sample.

The treatment for PAL includes surgery, combination chemotherapy, and radiation therapy. Although chemotherapy with rituximab is considered as an effective treatment, the 1-year survival rate is only 17.5%.[15] Case one in this study received chemotherapy alone. After four courses of chemotherapy, PET-CT showed no remission. Thus considering the possibility of developing drug resistance, another three courses of adjusted chemotherapy were given. Case two in our study received eight courses of chemotherapy (seven courses of chemotherapy with rituximab) after the surgery and presented stable disease. However, it is still worth exploring the necessity of maintenance chemotherapy. At present, there are several reports on new drugs such as nivolumab in DLBCL. Lesokhin AM et al demonstrated in a multicenter clinical trial that nivolumab achieved response rate of 36% in relapsed/refractory DLBCL (n = 11) patients, and only one patient experienced recurrence during a median follow-up of 6 months.[16] So further clinical trials are needed for early employ of immunological checkpoint inhibitors such as nivolumab in patients with higher expression of PD-L1 or resistance to primary chemotherapy.

In summary, PAL is a type of non-Hodgkin's lymphoma with low incidence and poor prognosis, and it is necessary to further explore the early use of immunological checkpoint inhibitors for patients with higher expression of PD-L1 and with rituximab-resistance.

ACKNOWLEDGMENTS

This work was supported by the National Science Foundation of China (No. 81700182) and the Natural Science Foundation of Shanxi (201601D202094).

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How to cite this article: Chen Y, He HS, Hu QF, Wang G. Adrenal diffuse large B-cell lymphoma with high PD-L1 expression: Two case reports and literature review. *J Clin Lab Anal*. 2020;34:e23173. https://doi.org/10.1002/jcla.23173