Primary bilateral adrenal lymphoma masquerading as a metastatic melanoma: An unusual presentation of a rare disease

J. Stephen Stalls [a],[*],[1], Anas Mohamed [a],[1], Masood Hassan [a], Kim Geisinger [b], Anuradha Kanungo [a], Moiz Vora [a], Anokhi Patel [b], Andrew Weil [b]

[a] East Carolina University, Department of Pathology and Laboratory Medicine, United States
[b] East Carolina University, Department of Internal Medicine, Division of Hematology/Oncology, United States

ABSTRACT

This report describes a 70-year-old male with bilateral primary adrenal lymphoma (PAL) characterized as non-germinal center diffuse large B-cell lymphoma (DLBCL). PAL is a very rare, aggressive disease with a poor prognosis. Our patient presented with B symptoms, chills, and nausea. Imaging studies of his abdomen revealed rapidly enlarging bilateral adrenal masses. Computed tomography (CT) guided left adrenal mass core biopsy showed diffuse sheets of neoplastic cells with irregular nuclear contours, vesicular to hyperchromatic chromatin, and prominent nucleoli. The neoplastic cells demonstrated an immunohistochemistry (IHC) profile consistent with DLBCL. Markers assessing for melanoma and neuroendocrine tumors were negative. Fluorescence in situ hybridization (FISH) revealed BCL6 rearrangement. The diagnosis of primary adrenal DLBCL, non-germinal center subtype, was rendered. The patient's chemotherapy is ongoing; six cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) induced significant clinical and radiological response.

The differential diagnosis is broad in patients with adrenal insufficiency and bilateral adrenal masses, and our case clinically centered on metastatic melanoma in the differential. Thorough pathologic evaluation of tissue, including an extensive IHC panel, was warranted for this patient due to the rarity of PAL and due to the morphologic overlap between melanoma and DLBCL.

1. Introduction

Primary involvement of adrenal glands by lymphoma is exceedingly rare, with approximately 200 cases reported in the literature [1]. According to the published literature, most experts agree that PAL constitutes a histologically proven lymphoma involving one or both adrenal glands [2]. There cannot be a prior history of lymphoma elsewhere, and if lymph nodes or other organs are involved, the adrenal lesions must be clearly dominant [2]. PAL accounts for less than 1% of primary extranodal non-Hodgkin's lymphoma cases [2], and carries a high frequency of concomitant adrenal insufficiency (61% of cases in one series) [2]. In approximately 70% of cases, PAL presents with bilateral adrenal involvement [1]. Non-germinal center DLBCL is the most common histology for PAL, comprising more than 70% of cases [2]. This is followed

by peripheral T cell lymphoma (7% of cases) [1]. Up to 40% of all new DLBCL cases are confined to extranodal sites, at least initially [3].

PAL is typically highly symptomatic and aggressive, usually affecting elderly men and presenting with large bilateral adrenal masses [2]. B-symptoms, adrenal insufficiency, and elevated serum lactate dehydrogenase are common [1]. Lymphadenopathy, hepatosplenomegaly, and bone marrow involvement are less common [1]. PAL may appear as either homogenous or heterogenous tumors on CT [1]. Though PAL has historically had a poor prognosis, the addition of rituximab to chemotherapy regimens has improved outcomes [1].

2. Case report

Our patient is a 70-year-old male with a history of melanoma of the

right mid-upper back treated by excision, benign multinodular goiter treated by left thyroid lobectomy, and Meniere's disease. His melanoma was characterized as superficial spreading type with level II invasion. Radial growth and early vertical growth were present. Ulceration, satellite lesions, vascular invasion, and neurotropism were absent. This was diagnosed approximately seven years before the following presentation:

He presented with a three-month history of intermittent chills, nausea, sweats, and unintentional weight loss. A CT scan revealed bilateral enlargement of the adrenal glands; no other masses were noted. The differential diagnosis included lymphoma, metastatic melanoma and primary adrenocortical carcinoma. Before biopsy was considered, endocrinology and infectious disease studies were completed to exclude competing primary adrenal or infectious etiologies. Workup for adrenal insufficiency, pheochromocytoma, and hyperaldosteronism was negative. Serological tests for human immunodeficiency virus (HIV) and tuberculosis were negative. He continued to have intermittent abdominal pain, nausea, and malaise, and presented to the ED with these symptoms. A follow up CT (approximately two months after his baseline CT) showed interval enlargement of both adrenal glands with possible bilateral hemorrhage. Endocrinology felt this put him at risk for developing adrenal insufficiency and placed him on steroids prophylactically. Three AM cortisol tests were within normal limits and no ACTH stimulation test is on file. Additionally, his vital signs were unremarkable at admission. His symptoms improved and he was discharged; however, one week later he was readmitted for fever, abdominal pain, and mental status changes. CT scan (Fig. 1A) and magnetic resonance imaging (MRI) (Fig. 1B) of his abdomen revealed splenomegaly and progressive bilateral adrenal enlargement measuring 10.3 cm on the left and 9.6 cm on the right, with heterogeneous attenuation and rounded configuration (reference adrenal gland measurements are approximately 7 cm long, 3 cm high, and 1 cm thick) [5].

CT-guided left adrenal mass core biopsy was performed. Microscopic examination of hematoxylin and eosin (H&E) stained slides showed diffuse sheets of medium to large neoplastic lymphoid cells with irregular nuclear contours, vesicular to hyperchromatic chromatin, and prominent nucleoli growing in a solid pattern with loose cohesion. Increased mitotic figures and tingible body macrophages were present (Fig. 2A, and B).

The IHC lymphoma panel showed neoplastic cells positive for CD45 (Fig. 2C), CD20 (Fig. 2D), PAX5 (Fig. 2E), BCL6 (Fig. 2F), BCL2 (Fig. 2G), and MUM1 (Fig. 2H). The neoplastic cells were negative for CD3 (Fig. 3A), CD10 (Fig. 3B), CD30 (Fig. 3C), and cyclin D1 (BCL1, Fig. 3D). A Ki67 proliferation index of 80% of the tumor cells was detected (Fig. 3E).

Negative SOX10 (Fig. 3F) along with negative inhibin (Fig. 3G) indicated that metastatic melanoma as well as primary adrenocortical tumors were unlikely diagnoses. Pan-cytokeratin did not highlight any tumor cells (Fig. 3H); therefore, metastatic carcinoma was unlikely. Pheochromocytoma was ruled out by negative SOX10 and negative neuroendocrine markers including synaptophysin (Fig. 3I) and chromogranin (Fig. 3J). Plasma metanephrine and normetanephrine were unremarkable. FISH revealed only BCL6 rearrangement (single-hit lymphoma); no MYC or BCL2 translocation was identified. The aggregate pathologic findings of H&E, IHC, and FISH studies confirmed a diagnosis of primary adrenal DLBCL, non-germinal center subtype. Clinical and radiographic studies did not identify evidence of lymphoma outside of the adrenal glands.

The patient received six cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and intrathecal chemoprophylaxis with methotrexate. Follow-up positron emission tomography (PET) scan after cycle 2 revealed significantly smaller partially calcified bilateral adrenal masses consistent with positive treatment response. The left and right adrenal masses measured up to 3.8 cm, and 2.9 cm, respectively. PET scan after cycle 4 demonstrated stable low-grade metabolic activity; on the left the SUV was estimated at 3.2 compared to 3.4 on prior exam, on the right the standard uptake value (SUV) was estimated at 2.8 compared to 2.5 on prior exam. PET scan after cycle 6 demonstrated slightly less avidity in the adrenal glands; FDG uptake at the left and right adrenal glands was about 2.3 SUV bilaterally. The patient is currently doing well clinically; he is tolerating his chemotherapy well and is not experiencing fevers, chills, night sweats, weight loss, nausea or vomiting.

3. Discussion

The incidence of adrenal masses detected by CT and autopsy can be as high as 4.4% and 9%, respectively [4]. Multiple neoplastic and non-neoplastic differential diagnoses should be considered for bilateral adrenal masses, including metastases, adrenocortical carcinoma, lymphoma, pheochromocytoma, adenoma, myelolipoma, adrenal hyperplasia, adrenal hemorrhage, and infections such as tuberculosis, histoplasmosis and blastomycosis [6]. In one retrospective review of 5638 melanoma patients with a median follow-up of 5.2 years, 1180 patients developed distant metastatic disease, including 154 (13% of the metastatic population) who developed adrenal metastasis [7]. Therefore, adrenal involvement in the setting of metastatic melanoma is an uncommon, but not extremely rare event.

Our patient's sex, age, and remote history of melanoma are risk
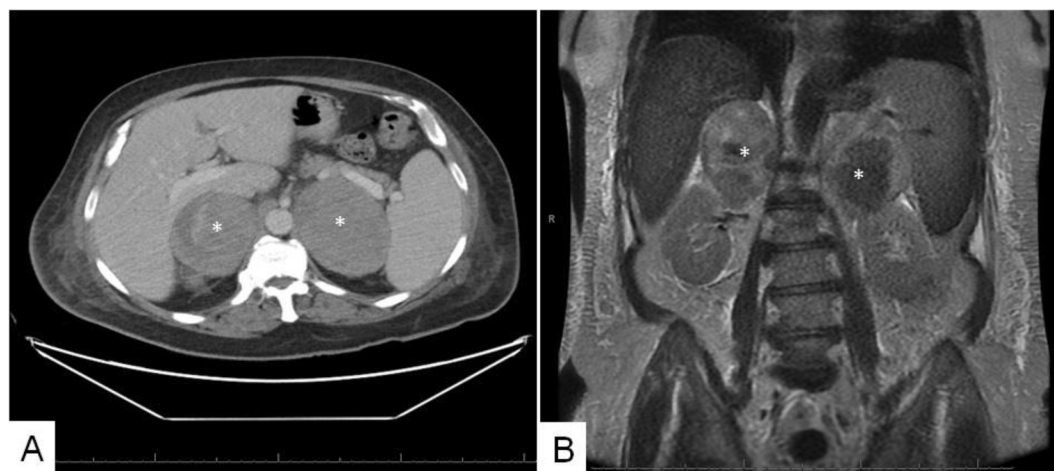

Fig. 1. CT scan (axial view) showing heterogeneous, hyperdense, bilateral adrenal masses measuring 9.6 × 6.5 cm on the right and 10.3 × 7.5 cm on the left (asterisks) (A). MRI image (coronal view) showing 8.9 × 6.5 cm right adrenal mass and 10.7 × 7.5 cm left adrenal mass (asterisks) demonstrate mixed intermediate and low T1 and T2 signals (asterisks) (B).
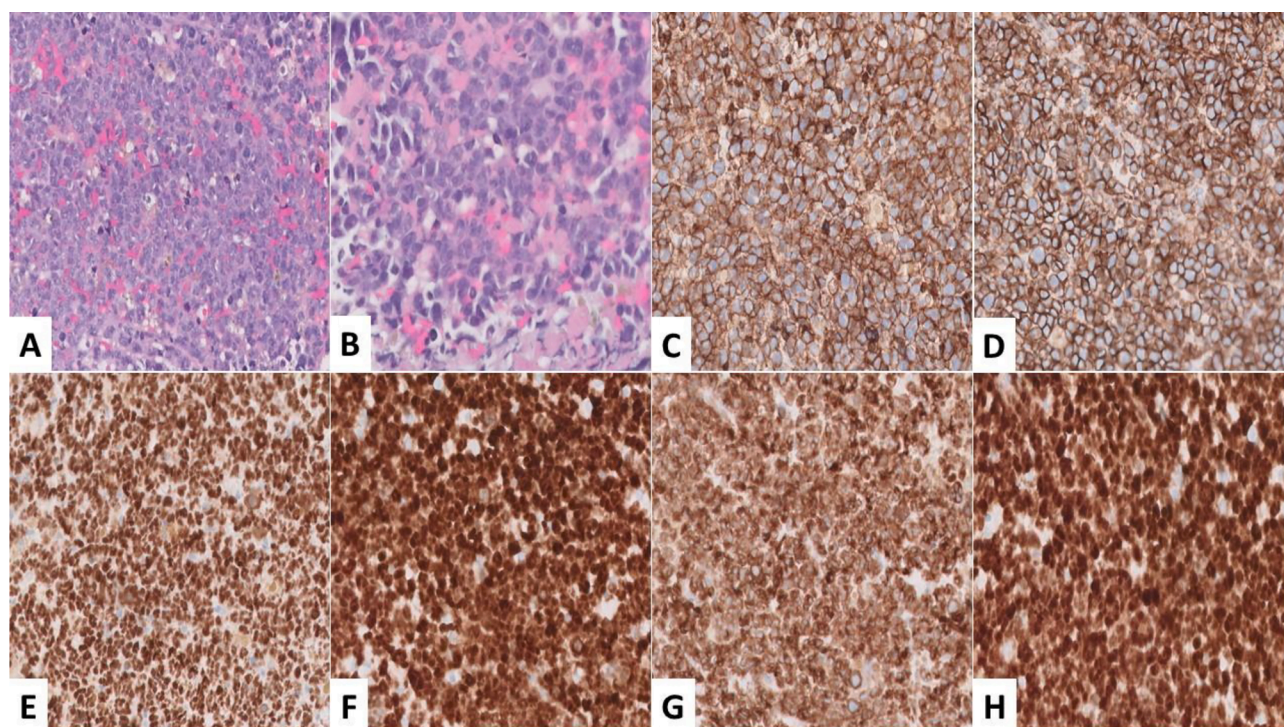
Fig. 2. Cores from adrenal glands are completely replaced by sheets of crowded basophilic cells (A). Medium to large lymphoid cells with irregular nuclear contours, vesicular to hyperchromatic chromatin, and prominent nucleoli are seen (B) (hematoxylin-eosin, original magnifications X200 (A) and X400 (B)). Neoplastic cells are positive for CD45 (C), CD20 (D), PAX5 (E), BCL6 (F), BCL2 (G), and MUM1 (H). (immunohistochemistry, original magnification X200 (C), (D), (E), (F) (G), and (H)).
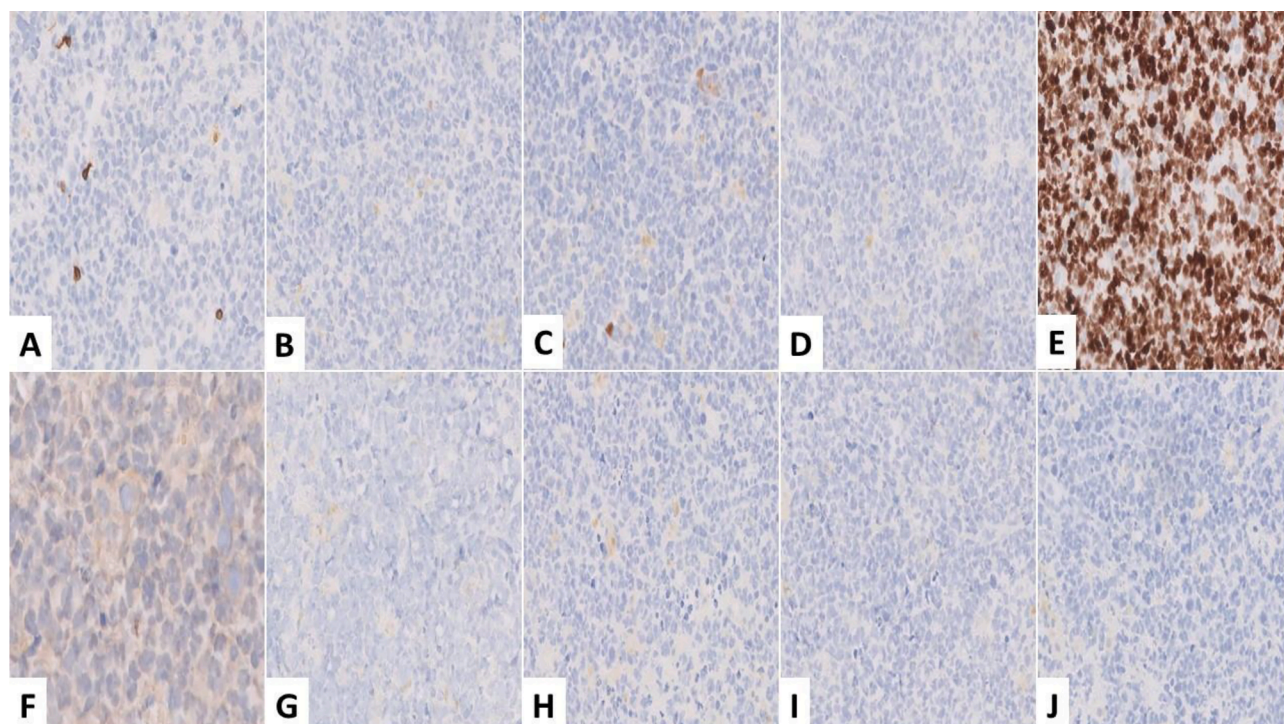

Fig. 3. Neoplastic cells are negative for CD3 (A), CD10 (B), CD30 (C), and cyclin D1 (BCL1, D). A Ki67 proliferation index of 80% of the tumor cells was detected (E). Additional negative markers include SOX10 (F), inhibin (G), pan-cytokeratin (H), synaptophysin (I), and chromogranin (J) (immunohistochemistry, original magnification X200 (A), (B), (C), (D), (E), (F) (G), (H), (I), and (J)).

factors for PAL. One literature review of 55 patients with PAL showed that the male to female ratio is 2.2:1. Elderly males are more commonly affected (average age at diagnosis was 65). Fifteen percent of cases had either concurrent or remote history of malignancy. The same review also identified autoimmune diseases as a significant association (13%) [8]. Interestingly, our patient did have a history of multinodular goiter and

Meniere's disease, which may be a consequence of autoimmune reactions [9]. Another significant risk factor for PAL is Epstein-Barr virus (EBV) infection, which is believed to play a role in the development of PAL [1]. Our patient was not tested for EBV by immunohistochemistry or any other modality, to the best of our knowledge.

It has been suggested that PAL is more likely to cause adrenal insufficiency (approximately 61% of cases) than metastatic cancers to the adrenal glands (approximately 25% in bilateral cases) due to the functional, cytokine-driven paracrine effect that lymphoma cells have in the adrenal gland microenvironment [1]. By contrast, metastatic tumors cause adrenal insufficiency more so by overgrowing and compressing normal adrenal tissue or compromising the vascular supply [1].

Some authors have attributed the commonness of adrenal insufficiency in PAL to publication bias [1]. Though our patient never had a low cortisol level, he may have well developed it without prophylactic steroids. Destruction of more than 90% of the adrenal gland may be required for adrenal insufficiency to become apparent [1]. Larger PALs have been documented without any evidence of adrenal insufficiency, and small PALs can be associated with adrenal insufficiency [1]. This suggests a weak or non-existent correlation between tumor size and adrenal insufficiency in PAL [1]. Our patient's tumor size appears to be relatively large, as one review showed a median size of 8 cm in greatest diameter, with a range of 5.7–10 cm in greatest diameter [1]. However, it should be noted that the CT abdomen adrenal measurements of 10.3 cm on the left and 9.6 cm on the right were taken two months after his baseline abdominal CT, which did not include exact measurements of the adrenal glands.

FISH of our patient's tumor cells revealed rearrangement of the 3q27 region of BCL6, which is the most common chromosomal translocation in DLBCL [3]. This translocation is more frequent in non-germinal center DLBCL, and may be associated with improved survival [3].

4. Conclusion

PAL is a very rare disease with a poor prognosis, and was quite a surprising diagnosis in our case. Given our patient's history and the rarity of PAL, recurrent/metastatic melanoma to the adrenal glands was the original working hypothesis. As the differential diagnosis is broad in patients with adrenal insufficiency and bilateral adrenal masses, and since melanoma can masquerade as many different histologies on H&E, our patient manifests the importance of a thorough pathologic evaluation.

5. Ethics statement

This study adhered to the guidelines set forth by the Office of Human Research Protection that is supported by U.S. Department of Health & Human Services. The patient's provider obtained telephone consent from the patient and this was documented in the patient's electronic medical record.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Rashidi, S.I. Fisher, Primary adrenal lymphoma: a systematic review, Ann. Hematol. 92 (12) (2013) 1583–1593, https://doi.org/10.1007/s00277-013-1812-3.

[2] N. Ram, O. Rashid, S. Farooq, I. Ulhaq, N. Islam, Primary adrenal non-Hodgkin lymphoma: a case report and review of the literature, J. Med. Case Rep. 11 (1) (2017) 108, https://doi.org/10.1186/s13256-017-1271-x. Published 2017 Apr 15.

[3] S. Swerdlow, E. Campo, N. Harris, et al., WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed., IARC, Lyon, 2017.

[4] W. Ovalle, P. Nahirney, F. Netter, Netter's Essential Histology, Elsevier, Philadelphia, 2007.

[5] D.T. Arnold, J.B. Reed, K. Burt, Evaluation and management of the incidental adrenal mass, Proc. (Bayl. Univ. Med. Cent). 16 (1) (2003) 7–12, https://doi.org/10.1080/08998280.2003.11927882.

[6] P. Gupta, A. Bhalla, R. Sharma, Bilateral adrenal lesions, J. Med. Imaging Radiat. Oncol. 56 (6) (2012) 636–645, https://doi.org/10.1111/j.1754-9485.2012.02435.x.

[7] E.A. Mittendorf, S.J. Lim, C.W. Schacherer, et al., Melanoma adrenal metastasis: natural history and surgical management, Am. J. Surg. 195 (3) (2008) 363–369, https://doi.org/10.1016/j.amjsurg.2007.12.018.

[8] J. Wang, N.C. Sun, R. Renslo, et al., Clinically silent primary adrenal lymphoma: a case report and review of the literature, Am. J. Hematol. 58 (2) (1998) 130–136, https://doi.org/10.1002/(sici)1096-8652(199806)58:2<130::aid-ajh8>3.0.co;2-t.

[9] Ménière's Disease. National Institute on Deafness and Other Communication Disorders. https://www.nidcd.nih.gov/health/menieres-disease. Published 2021. Accessed June 12, 2021.