CASE REPORT

Mantle cell lymphoma presenting as bilateral adrenal huge masses

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SUMMARY

We present a middle-aged woman complaining of weakness, lethargy and weight loss for 6 months. Positron emission tomography (PET)/CT scan revealed huge bilateral adrenal masses with intense 18F-fluorodeoxyglucose avidity. Biopsy and immunohistochemical staining were compatible with mantle cell lymphoma (MCL). The patient received six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) followed by four cycles of intrathecal methotrexate chemotherapy. Bone marrow aspiration biopsy was performed for initial staging and also before bone marrow transplantation. Follow-up PET/CT scan after completion of chemotherapy and before bone marrow transplantation demonstrated complete metabolic response with no evidence of abnormal metabolic activity in either adrenal gland or bone marrow. MCL has an aggressive nature and is usually considered incurable; however, there have been a few reports indicating favourable treatment response when MCL is rarely arising from the adrenal glands. Dramatic response of a primary adrenal MCL to R-CHOP is documented in this case.

BACKGROUND

Mantle cell lymphoma (MCL) is a distinct subtype of non-Hodgkin's lymphoma (NHL) accounting for 4%–6% of the new NHL cases in the USA annually.¹ MCL ranges from indolent to aggressive clinical presentations and is considered incurable with standard therapies.² The high proliferation rate of MCL cells may contribute to disease aggressiveness and inferior clinical outcome.^{3,4}

Primary adrenal gland lymphoma is a rare type of extranodal lymphoma with even rarer bilateral adrenal involvement and the most common histological subtype being diffuse large B-cell lymphoma (DLBCL).⁵ Primary adrenal involvement by MCL is unusual and is associated with a small number of DLBCL cases, where it carries an increased risk for central nervous system dissemination,⁶ and only a few cases have been reported in the medical literature.⁷

Here, we report a very rare case of primary bilateral adrenal gland MCL presenting as huge and intensely 18F-fluorodeoxyglucose (FDG)-avid masses with dramatic response to R-CHOP (rituximab, cyclophosphamide, doxorubicin,

vincristine and prednisone) chemotherapy documented by post-treatment FDG positron emission tomography (PET)/CT scan.

CASE PRESENTATION

A 55-year-old woman with bilateral huge adrenal masses was referred for pretreatment PET/CT scan. Her chief complaint was weakness, intermittent fever and lethargy with weight loss for the past 6 months. Previous medical history was significant for episodes of hypotension and hyperlipidaemia. Patient denies any cough/night sweat/weight loss/recent travel to tuberculosis (TB)-endemic area or exposure to TB contacts to suggest TB infection. The patient also denies any loss of appetite/weight loss or change in bowel habits to suggest any malignancy. The patient's family history was also negative regarding malignancy.

On physical examination, there was no evidence for lymphadenopathy or splenomegaly. There was no feature of skin hypopigmentation. The initial laboratory tests demonstrated electrolyte imbalances such as hyperkalaemia (K:5.4 mEq/L) and hyponatraemia (Na:125 mEq/L). Synacthen test was performed which showed poor adrenal response consistent with adrenal insufficiency.

A multidetector CT (MDCT) scan of the thorax, abdomen and pelvis demonstrated huge bilateral adrenal gland masses measuring 103×122 mm on the left side and 78×120 mm on the right side (in greatest transaxial dimension). The MDCT scans were otherwise unremarkable.

Preliminary pathology report from the right adrenal mass core biopsy was consistent with high-grade lymphoma. The sections demonstrated sheets of lymphoid cells with large vesicular nuclei and scanty cytoplasm containing many apoptotic bodies in between. No necrosis was identified. The bone marrow aspiration/biopsy (BMA) was also performed for initial staging which was reported as no definite evidence of lymphomatous involvement (figures 1 and 2).

Subsequent immunohistochemical (IHC) staining demonstrated positive LCA (Leukocyte Common Antigen) and CD20 markers in sheets of atypical lymphoid cells, weakly positive CD5 marker in sheets of atypical lymphoid cells. BCL2, MUM1 and cyclin D1 were also positive in sheets of lymphoid cells. Ki-67 demonstrated proliferative capacity in 80% of lymphoid cells, while CD138, CD3, CD34, CD10, TdT, BCL6 markers were negative.

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Figure 1 H&E stained slide×20: Proliferation of small-sized to medium-sized lymphoid cells with irregular nuclear contours.

According to IHC results, the phenotype of tumour cells was non-germinal centre type. These IHC findings confirmed diagnosis of primary adrenal gland MCL.

Although aberrant expression of SOX-11 could play an oncogenic role in the pathogenesis of classic MCL,⁸ the SOX-11 IHC was not available for pathology evaluation at the time of diagnosis and, unfortunately on subsequent review, there was no tissue left in the paraffin block for evaluation of SOX-11 by IHC method.

FDG PET/CT scan was performed afterwards for initial staging which demonstrated intensely increased bilateral adrenal FDG uptake, whereas the remainder of the PET/CT study including axial skeleton bone marrow were unremarkable (figure 3).

The patient's Eastern Cooperative Oncology Group status was zero according to the clinical evaluation by the referring oncologist, and the patient's International Prognostic Index (IPI) score was considered as 1 because of raised lactate dehydrogenase.

After confirmation of primary adrenal MCL diagnosis, the patients underwent six cycles of chemotherapy treatment with R-CHOP followed by four cycles of intrathecal methotrexate chemotherapy.

Figure 2 Immunohistochemical-stained slides×20: Positive reaction for CD20, cyclin D1, Bcl2 and CD5.

Figure 3 Pretreatment positron emission tomography/CT scan demonstrating huge and intensely 18F-fluorodeoxyglucose-avid bilateral adrenal masses.

Postchemotherapy FDG PET/CT was negative demonstrating dramatic decrease in size of bilateral adrenal masses with no evidence of FDG avidity. These findings on PET/CT were interpreted as complete metabolic response (CMR) by the referring oncologist (figure 4).

INVESTIGATIONS

The patient was referred for autologous stem cell transplantation (ASCT); therefore, pretransplantation bone marrow aspiration was repeated which was also reported unremarkable.

DIFFERENTIAL DIAGNOSIS

In most cases, bilateral adrenal masses represent benign bilateral adrenocortical disease including bilateral adenomas, macronodular hyperplasia or distinct bilateral nodules with normal or atrophic intervening cortex. The possibility of metastases (especially in patients with known malignancy), adrenal lymphoma or bilateral pheochromocytomas should also be considered. Moreover, bilateral adrenal masses may represent co-occurrence of different entities, such as adenoma, pheochromocytoma, cyst, myelolipoma and adrenocortical carcinoma.

Additional differential diagnosis for MCL include: chronic lymphocytic leukaemia, hairy cell leukaemia, diffuse large cell and follicular lymphoma, follicular centre cell lymphoma, lymphoplasmacytic lymphoma, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, non-neoplastic hyperplasias (Castleman disease, mantle zone hyperplasia, reactive follicular hyperplasia) and small lymphocytic lymphoma.

Figure 4 Post-treatment positron emission tomography/CT scan demonstrating no evidence of residual 18F-fluorodeoxyglucose-avid adrenal lesion compatible with complete metabolic response.

TREATMENT

The patient received six cycles of R-CHOP chemotherapy after confirmation of MCL diagnosis followed by four cycles of intrathecal methotrexate chemotherapy.

The patient received ASCT following her unremarkable post-chemotherapy BMA.

OUTCOME AND FOLLOW-UP

Excellent response to R-CHOP chemotherapy and intrathecal methotrexate was documented by post-treatment PET/CT scan which demonstrated CMR with no evidence of residual adrenal mass or residual metabolically active disease.

The patient is currently on maintenance rituximab treatment (one intravenous perfusion of 375 mg/m² of body surface area administered every 2 months).

The most recent laboratory panel was with normal range except for lactate dehydrogenase (LDH) which was reported as 442 U/L and will be followed.

The patient suffers from persistent severe adrenal insufficiency and currently is also on corticosteroid replacement.

DISCUSSION

MCL is a subtype of B-cell type NHL and its clinical, biological and genetic properties (chromosomal translocation t(11; 14) (q13; q32)) resulting in overexpression of cyclin D1 which is characteristic of MCL but not unique.⁷⁻⁹ Therefore, virtually all cases are diagnosed in advanced stages and the median life expectancy ranges from 3 to 7 years.¹⁰ Tissue biopsy from the involved lymph nodes or extranodal sites is essential for diagnosis; however, the European Society of Endocrinology recommends complementary diagnostic methods such as imaging studies and hormonal assessment for bilateral adrenal masses.¹¹ For this purpose, CD5 and CD19 markers should be positive and CD23 should be negative in IHC staining for MCL diagnosis confirmation.¹²

The incorporation of PET scans into the clinical management of MCL has not been studied systematically. According to previous studies, the MCL is considered to be highly FDG avid on PET scans.¹³⁻¹⁴ Study conducted by Hosein *et al* in 2011 revealed that PET scan does not meaningfully contribute to staging or surveillance of MCL patients; however, there was a trend toward improved survival in patients who had a negative end-of-therapy PET scan.¹⁵ MCL has a high frequency of extranodal site involvement for which PET is much more useful in identifying than is standard CT scan imaging; however, PET should not be used for routine post-treatment surveillance.

Because of unique clinical features, aggressive nature and unresponsiveness to medical treatment, MCL is generally considered incurable.¹⁰ However, in our study, six cycles chemotherapy with R-CHOP followed by four cycles of intrathecal methotrexate resulted in dramatic decrease in size and resolution of abnormal metabolic activity in bilateral adrenal MCL consistent with CMR. Aravamudan *et al* recently reported a case of primary bilateral adrenal MCL treated with R-CHOP chemotherapy and favourable clinical response, remaining in complete remission for 5 months after completion of chemotherapy.⁵ A study by Hashimoto *et al* reported a case with MCL markedly infiltrated into adrenal glands with adrenal insufficiency. In this study, the diagnostic method was based on biopsy and IHC staining (atypical cells showed CD5+, cyclin D1+, CD19+, CD20+ and HLA-DR+). Finally, bilateral adrenal masses dramatically reduced in size after CHOP chemotherapy with hydrocortisone supplementation and no rituximab maintenance (RM).¹⁶⁻¹⁷

MCL is highly responsive to a variety of therapies and achievement of remission occurs for most cases, but the difficulty is in maintaining the disease remission. Patients with MCL usually respond to initial combination chemotherapy, but the disease inevitably relapses and often follows an aggressive course.¹⁸ In a recent study, Le Gouill *et al* recommended that four courses of dexamethasone, high-dose cytarabine and cisplatin plus ASCT, without total body irradiation followed by RM (one infusion every 2 month for 3 years) is a new standard of care for young patients with MCL.¹⁹

Rituximab-based primary treatment has been shown to significantly improve complete remission rate. The addition of ASCT has also improved progression-free survival (PFS) although data regarding potential overall survival (OS) benefits are not clear.

Complete remission and minimal residual disease states are predictive of clinical outcome. RM after SCT has also been shown to significantly improve PFS and OS.²⁰

According to other studies, age, tumour size, adrenal insufficiency, lactate dehydrogenase level and performance status of the patient can significantly influence the MCL prognosis.²¹⁻²²

The MCL International Prognostic Index is used for MCL prognostication. In a more simplified version, the patient's age, LDH level and white cell count are considered to determine the IPI.²³ A high Ki-67 proliferation index (PI) in neoplastic cells is associated with poor survival in MCL. According to a study by Jeong *et al*, the 20% cut-off value for the Ki-67 PI was clinically meaningful, regardless of bone marrow involvement of MCL. For patients with bone marrow involvement, the statistically significant cut-off value increased to 30%.²⁴

Finally, Mosoz *et al* on their review on 10 cases of primary adrenal DLBCL concluded that the potentially poor outcome of primary adrenal lymphoma might be related to the bulky tumour size at presentation, non-germinal centre B-cell phenotype and frequent BCL-6 gene rearrangement.²⁵

Learning points

- ▶ Primary adrenal gland mantle cell lymphoma (MCL) is a very rare pathology.
- ▶ Early work-up including biopsy, immunohistochemical staining and 18F-fluorodeoxyglucose (FDG) PET/CT for initial staging are recommended and immunochemotherapy is the preferred treatment option.
- ▶ The risk of central nervous system dissemination is unknown for MCL, although would be high for adrenal involvement by diffuse large B-cell lymphoma.
- ▶ FDG PET/CT may be a valuable non-invasive imaging method for initial staging and treatment response evaluation in primary adrenal MCL.

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