

CASE REPORT

A rare case of plasmablastic lymphoma with MDM2 overexpression and amplification

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ABSTRACT

We describe a challenging differential diagnosis of a poorly differentiated tumor arising in the abdominal cavity of a 76-year-old woman. After histological and immunohistochemical analysis the differential diagnosis between a plasmablastic lymphoma (PBL) and a dedifferentiated liposarcoma remained. Molecular testing was necessary to make a definite diagnosis of PBL. To the best of our knowledge, this is the first report in literature of PBL with MDM2 overexpression and amplification. Awareness of this finding could prove useful for appropriate patient management.

Key Words: Plasmablastic lymphoma, Dedifferentiated liposarcoma, Sigmoid, Elderly patient, MDM2

1. INTRODUCTION

Plasmablastic lymphoma (PBL) is a rare and aggressive variant of diffuse large B-cell lymphoma (DLBCL).^[1] Initially, it was described in patients with acquired immunodeficiency syndrome (AIDS).^[2] Over the years, PBL has also been diagnosed in patients with other causes of immunodeficiency, or sporadically in patients without known immunodeficiency, like in our report.^[3-5] The most common localization is the oral cavity but other localizations are described.^[1,3] A poorly differentiated tumor in the abdominal cavity has a broad differential diagnosis, which could be narrowed by using immunohistochemistry. Overexpression of MDM2, caused by *MDM2* amplification made it impossible to differentiate between PBL and a dedifferentiated liposarcoma. Additional genetic testing led to a diagnosis of PBL. The aim of this report is to draw attention to this tumor entity, the recognition of which can be challenging.

2. CASE REPORT

A 76-year-old woman presented with urinary incontinence. She had been complaining of vague abdominal pain, without nausea, anorexia or weight loss since 6 weeks. Recently, she noticed changes in bowel habits. The patient was suffering from Parkinson's disease. Her previous medical history contained a right shoulder and elbow surgery, sterilization and bilateral cataract surgery. During physical examination, a suprapubic mass was palpable and edema of the lower extremities was noticed. Magnetic resonance imaging (MRI) revealed a large mass with a diameter of 17.9 cm that completely entrapped the sigmoid colon and both ovaries. The tumor invaded the wall of the bladder, the uterus and the small bowel. There was also peritoneal, mesenterial and serosal tumor spread. Sigmoidoscopy showed a narrowed and fixated sigmoid.

During laparotomy biopsies of the abdominal mass were

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obtained. They revealed a poorly differentiated tumor with a dis-cohesive growth pattern (see Figure 1A). Nests, trabeculae and papillae were recognizable. The tumor cells had an abundant cytoplasm and oval nuclei. The nuclei were hyperchromatic or vesicular with prominent central nucleoli or several small nucleoli. Scattered mitotic and apoptotic bodies were present. There were no obvious plasmacytoid

features. The histological features seen on the biopsy can be found in a variety of tumors. The pathological differential diagnosis included poorly differentiated metastatic carcinoma, metastatic malignant melanoma, DLBCL, Burkitt lymphoma, anaplastic large cell lymphoma (ALCL) and dedifferentiated liposarcoma.

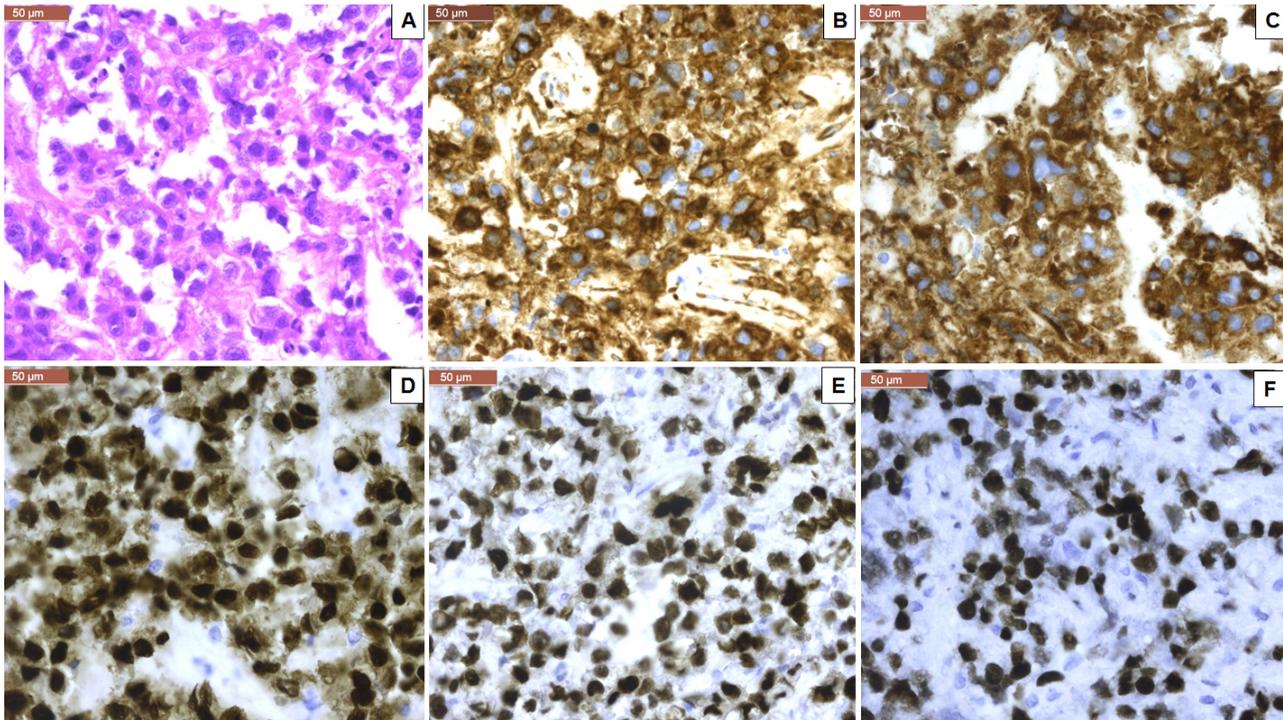


Figure 1. (A) Hematoxylin & Eosin stain show a dis-cohesive growing tumor with large tumor cells. The cells have an abundant cytoplasm and an enlarged hyperchromatic or vesicular nuclei with prominent nucleoli. The tumor cells show membranous and cytoplasmic expression of CD138 (B) and EMA (C) and strong nuclear expression of MUM1 (D) and MDM2 (E). There is nuclear expression of C-MYC in a large subset of tumor cells (F). All images are at 40× magnification.

By immunohistochemistry, the neoplastic cells were strongly positive for EMA, CD138, MUM1, MDM2, GATA-3 and C-MYC (see Figure 1B-F). Cytokeratin AE1/AE3 was weakly positive. No expression of CK7, CK20, TTF1, CDX2, CEA, WT1, calretinin, ER, PR, chromogranin A, synaptophysin, inhibin, SMA, desmin, S100, melan A, CD20, CD3, CD45, CD4, CD5, CD30, CD35, CD21, CD23, CD 56, CD68, CD79a, CD34, ERG, CD1a, MPO, PAX5, PAX8, HHV8 and *in situ* hybridization for EBER was negative. There was aberrant expression of p53 in 10% of the tumor cells.

Initially, a poorly differentiated carcinoma was the preferential diagnosis because of the morphology of the tumor cells and the clinical presentation. There was expression of EMA and a weak expression of cytokeratin AE1/AE3 and all other epithelial markers were negative. Although loss of epithelial markers can be seen in poorly differentiated carcinomas, it

should always warrant pathologists to perform further immunohistochemical staining to exclude other tumors, which was done in this case. Metastatic malignant melanoma was ruled out by the absence of markers like S-100 and Melan A. Absence of the general B-cell marker CD20 excluded DLBCL and Burkitt lymphoma. CD30 and T cell markers like, CD3 and CD5 were negative, which ruled out ALCL. The tumor cells did show expression of CD138 and MUM1, suggesting the possibility of a plasma cell derived neoplasm such as PBL or plasmacytoma. The clinical course and the morphology of the neoplastic cells did not fit within the diagnosis of a plasmacytoma. Kappa and lambda immunostains were not contributive. However, the neoplastic cells also exhibited nuclear positivity for MDM2; which is typically seen in well-differentiated and dedifferentiated liposarcoma. After morphologic and immunophenotypic analysis, the dif-

ferential diagnosis between a dedifferentiated liposarcoma and PBL remained, and we proceeded with molecular testing to make a diagnosis. FISH analysis showed *MDM2* amplification in 65% of cells. This finding supported the diagnosis of a dedifferentiated liposarcoma. However, an additional FISH test for *CDK4* amplification turned out to be negative, showing only gain of 1 to 3 copies of *CDK4* in 63% cells. The absence of *CDK4* amplification is unusual for the diagnosis of dedifferentiated liposarcoma. PCR for amplification of the *IgH* and *Ig-kappa* genes showed monoclonal gene rearrangement, supporting the diagnosis of a PBL. The C-MYC protein was overexpressed in the absence of an IG-MYC translocation, related to a gain of 1 or 2 copies of C-MYC in a subset of cells, as evidenced by FISH. At time of presentation, the disease was diagnosed as a PBL stage IV because it invaded the abdominal organs. A bone marrow biopsy was not performed. HIV serology was negative. The patient did not take any immunomodulatory drugs or was not known with an underlying autoimmune- or lymphoproliferative disorder or other malignancy.

Because of the patients old age and because she was already suffering from Parkinson's disease there was opted to treat her with CHOP chemotherapy. Six courses of standard CHOP chemotherapy were administered: cyclophosphamide (750 mg/m², day 1), doxorubicin (50 mg/m², day 1), vincristine (1.4 mg/m², day 1) and prednisone (100 mg, days 1-5) (CHOP) chemotherapy were administered. Computed tomography (CT) of the abdomen and thorax after 3 courses of CHOP showed partial therapy response with residual abdominal lymphoma localization. After 6 courses of CHOP the CT of the abdomen and thorax showed massive tumor progression. The patient passed away 8 months after the initial diagnosis.

3. DISCUSSION

We present a case of a 76-year-old woman who was diagnosed with a PBL stage IV, arising in her abdominal cavity. The tumor overexpressed en showed amplification of *MDM2*, which made it a difficult differential diagnosis with a dedifferentiated liposarcoma. The aim of this report is to describe this challenging differential diagnosis and to draw attention to the possibility of PBL to have amplification in *MDM2*.

PBL is a rare and aggressive B-cell non-Hodgkin lymphoma. Initially it was described in the oral cavity of AIDS patients. PBL accounts for approximately 2.6% of all AIDS-related lymphomas.^[1] In the initial report 15 of the 16 patients who had PBL were infected with HIV.^[2] Over the years, PBL has been reported in patients with other causes of immunodeficiency such as organ transplantation, lymphoproliferative or autoimmune disorders.^[3,4] PBL also occurs in patients

without known immunodeficiency. The majority of these patients are 50 years or older at time of diagnosis suggesting that age-related immuno-senescence can lead to lymphoma development.^[3,5] The majority of patients with PBL are men, particularly in the HIV-positive subgroup. The HIV-negative patients present at an older age (mean age, 58 years) than HIV-positive patients.^[1] Most patients have an advanced stage at the time of diagnosis.^[6] PBL is an aggressive lymphoma with a relapsing clinical course and a short median overall survival, varying between 7 and 12 months.^[7,8] Because of the aggressive nature of PBL intensive chemotherapy like EPOCH, hyper-CVAD or CODOX-M/IVAC is recommended.^[8] Our patient was treated with CHOP because of her old age and Parkinson's disease. Recent guidelines consider this an inadequate therapy although survival benefit of a more intensive chemotherapy is controversial.^[8]

In the initial report by Delecluse and co-workers, all patients presented with lesions in the oral cavity.^[2] Commonly affected extra-oral sites are the gastrointestinal tract, lymph nodes and skin. Other less common sites are the central nervous system, paranasal sinuses, mediastinum, lungs, liver, testis, heart, eye, soft tissue and bone marrow.^[1,3] HIV-positive patients more commonly present with lesions in the oral cavity.^[1,7] This might be due to the high incidence of premalignant lesions in the oral cavity of this subgroup of patients. They also have more common Epstein-Barr virus (EBV), human herpesvirus-8 (HHV-8) and human papillomavirus (HPV) infections in the oral cavity.^[7]

The majority of the PBLs are EBV positive.^[1] EBV-positive status is associated with a better overall survival.^[6,9] It has been reported that EBV-negative PBL in immunocompetent patients preferentially arises in the gastro-intestinal tract or the oral cavity, whereas EBV-positive PBL are mostly found in the nasal cavity.^[3] In our case the PBL was EBV negative and located in the abdomen with involvement of the gastro-intestinal (sigmoid wall) and urogenital tract. So far, only one other case with involvement of the sigmoid has been described.^[10] The majority of PBLs have aberrations of C-MYC, either gains or translocation, and all showed overexpression of C-MYC.^[9] The impact of C-MYC rearrangements on outcome is more controversial.^[3,9] In our case there was a strong expression of C-MYC but FISH analysis did not show C-MYC amplification. However, there was a strong nuclear expression of *MDM2* and FISH analysis showed *MDM2* amplification in a large portion of cells. *MDM2* can be overexpressed in a variety of malignancies, including B-cell non-Hodgkin lymphoma. In our respected literature search we didn't found a case of PBL with *MDM2* overexpression. *MDM2* is a negative regulator of the tumor suppressor p53. The impact of *MDM2* overexpression on prognosis in B-

cell non-Hodgkin lymphoma is inconsistent.^[11-14] MDM2 overexpression can be caused by increased transcription and translation, reduced degeneration or amplification. Except for liposarcoma amplification of *MDM2* is rarely the cause of MDM2 overexpression.^[12] We described a case of PBL with *MDM2* amplification. This amplification causes strong nuclear expression of MDM2, which made it impossible to differentiate between PBL and dedifferentiated liposarcoma without molecular tests. The hallmark of the latter tumor is the amplification of the *MDM2* and *CDK4* genes. Dedifferentiated liposarcoma most typically arises in the retroperi-

toneum and can show a very heterogeneous morphology.

4. CONCLUSION

In summary, we have described a challenging differential diagnosis between PBL and dedifferentiated liposarcoma. Histology and immunochemistry can be confusing and genetic analysis is essential for the final diagnosis. Awareness of these findings is important in the diagnostic process of a poorly differentiated tumor in the abdomen.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare that they have no competing interests.

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