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Case report

Long-term spontaneous regression of Stage IV diffuse large B-cell lymphoma

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Diffuse large B cell lymphoma (DLBCL) is an aggressive disorder accounting for >30% of all lymphomas. Its prognosis is poor due to a high relapse rate. Spontaneous regression (SR) in DLBCL is rare, with only a few reported cases. Moreover, almost all of these were low-grade lymphomas with an average SR duration of 13 mo. As the cause of SR is unknown, there are many theories such as trauma, infection, medication, and an antitumor immune response. We present a patient with progressive DLBCL who demonstrated SR for >42 mo. Although treatment for lymphoma usually starts soon after diagnosis, insights into SR of lymphomas may lead to new treatment strategies.

Keywords: Spontaneous regression, diffuse large B-cell lymphoma, long-term remission

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is an aggressive lymphoproliferative disorder accounting for >30% of all lymphomas. Although DLBCL is commonly found in the lymph nodes, approximately 30% of patients have extranodal DLBCL in organs such as the small intestine, mediastinum, thyroid, adrenal, breast, uterine, kidney, and testis.[1] Despite anthracycline-based chemotherapy, including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), the prognosis of DLBCL is poor due to a high relapse rate.[2] However, spontaneous regression (SR), *viz*., partial or complete disappearance in the absence of all treatment,[3] is reported in different types of lung cancers,[4-6] esophageal cancer,[7] breast cancer,[8] melanoma,[9] and neuroblastoma.[10,11] SR occurs in low grade lymphomas[12,13] and in limited stages (Ann Arbor stage I and II) DLBCL,[14-16] but in advanced stage (Ann Arbor stage III and IV) DLBCL it is extremely rare.[17] We present a patient with stage IV advanced stage DLBCL and SR of all identified lesions, ~1 mo after biopsy and positron emission tomography – computed tomography (PET-CT) diagnosis, that persisted for >42 mo. We include a review of advanced stage DLBCL in other patients with SR.

CASE PRESENTATION

A 76-year-old woman visited a local hospital because of vulvar discomfort in March 2017. Simple digital examination revealed a 3 cm mass in the anterior wall of the vagina centered on a point 2 cm from the vaginal introitus and 7 cm from the cervix, with protrusion into the lumen. The uterus and adnexae were unremarkable. Needle-aspiration material strongly suggested malignancy. The patient was referred to our hospital for further evaluation in April 2017.

She had gastric adenocarcinoma that was treated surgically >40 y before, without relapse. She had never smoked. No one in her family had a history of malignant disease. Vaginal and abdominal sonography demonstrated blood flow in the mass without other remarkable findings. No pertinent abnormalities were found on laboratory examination. Chemiluminescent enzyme immunoassay found no evidence of human immunodeficiency virus (HIV)-1 or -2 infection. In June 2017, positron emission tomography – computed tomography (PET-CT) revealed uptake in the vagina with a maximal standardized uptake value (SUV) of 47.08 and in the right lung (middle lobe) with an SUV of 37.10 (Figure 1A). Histopathologic examination of a core needle biopsy specimen from the vaginal mass found diffuse proliferation

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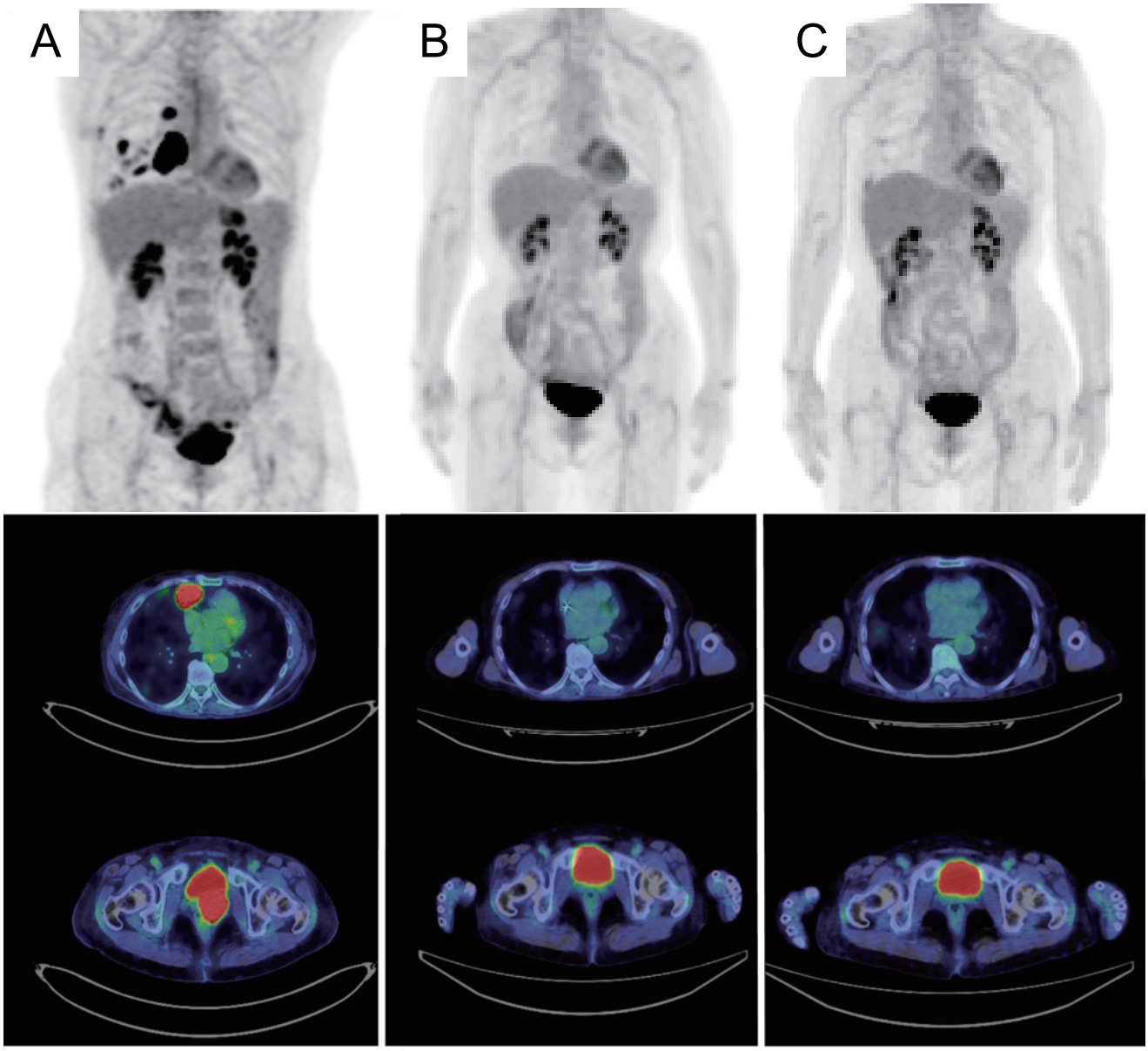

Fig. 1. Changes over time in PET-CT images. (***A***) Abnormal accumulation of fluorodeoxyglucose in the right lung (middle lobe), 30 mm in diameter, with a standardized uptake value (SUV) of 37.10, and a vaginal mass 40 mm in diameter before biopsy, with a maximal SUV of 47.08. (***B***) No abnormal accumulation of fluorodeoxyglucose 2 mo after the first PET-CT study. (***C***) No abnormal accumulation of fluorodeoxyglucose 1 y after the first PET-CT study.

of normal-to-large-sized lymphoid cells with irregular nuclei and features of apoptosis (Figure 2A and 2B). Elements of lymph node architecture were not discerned. On immunostaining, these lymphoid cells expressed CD10, CD20 (Figure 2C), Myc (>90%), and Bcl-6, without expression of Bcl-2, cyclinD1, or MUM1, consistent with germinal-center (GC) B-like DLBCL. The Ki-67 labeling index was evaluated at 90%. There was no split-signal for MYC and BCL-2 by fluorescence *in situ* hybridization. The lymphoma cells did not express programmed death ligand 1 (PD-L1) (Figure 2D). CD8-expressing ($CD8^+$) T cells in small numbers were scattered within the tumor (Figure 2E). Epstein-Barr virus-encoded small RNA (EBER) sequences were not demonstrable by *in situ* hybridization (Figure 2F). Material obtained on lung-mass biopsy was insufficient for a diagnosis.

These findings indicated of DLBCL, not otherwise specified, according to the World Health Organization 2016 classification. Bone marrow examination revealed no abnormal cells. The patient's disease was classified as Ann Arbor IVA advanced stage lymphoma, with an international prognostic index of intermediate risk.

On hospital admission for R-CHOP therapy in July 2017, the patient's general condition appeared unchanged. She had no interim febrile illness and was not taking any medications. However, "baseline" computed tomography revealed no lesions in the pelvic soft tissues or the right lung. We concluded that her DLBCL spontaneously regressed. She was discharged without treatment but with an appointment for

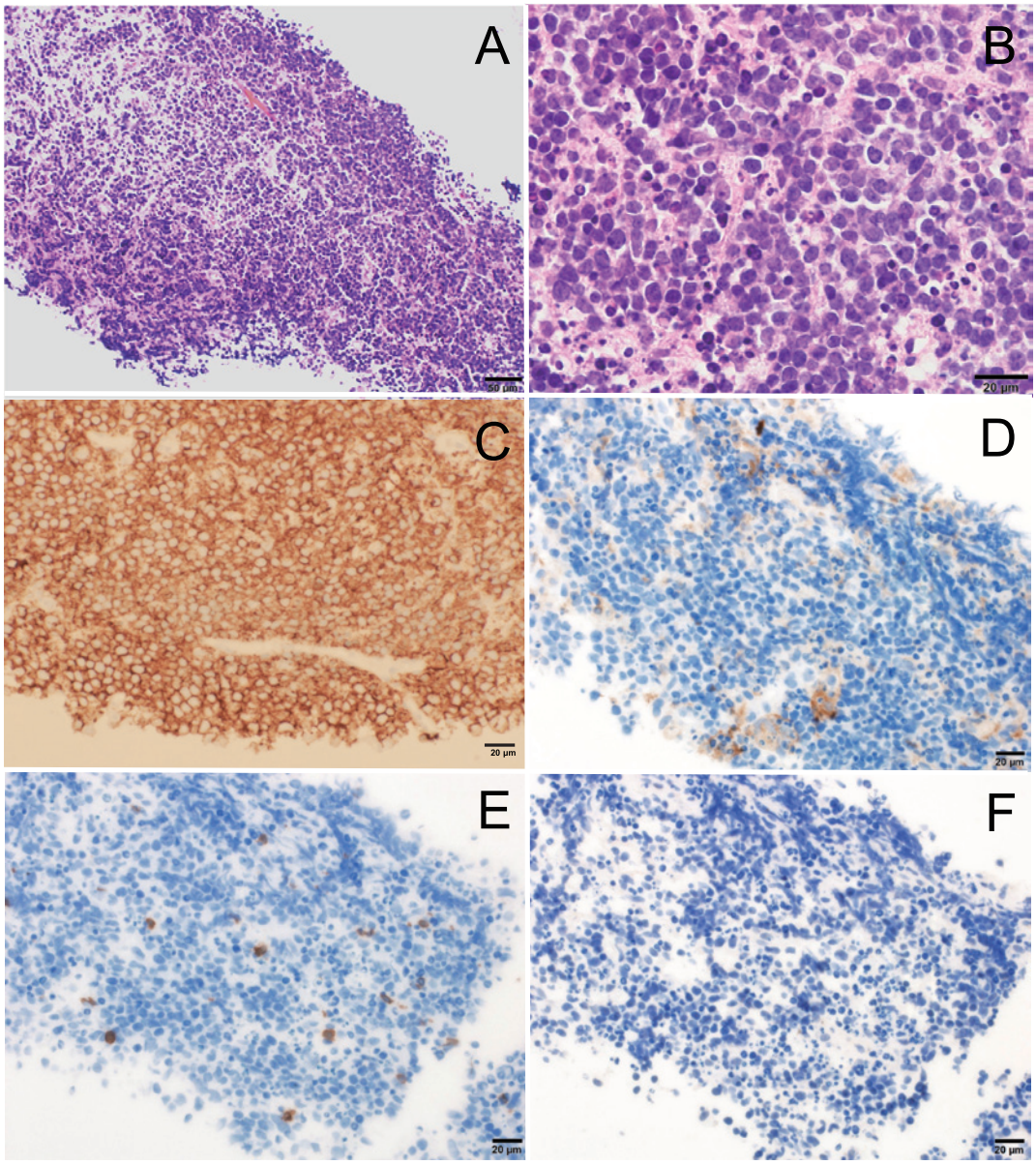

Fig. 2. Photomicrographs of the vaginal-mass biopsy specimen. (***A***) Diffuse proliferation of lymphoid cells (hematoxylin-eosin [H-E], original magnification x200). Scale bar, 50 µm. (***B***) Diffuse proliferation of medium-sized to large lymphoid cells with irregular nuclei and features of apoptosis (H-E, x400). Scale bar, 10 µm. Immunohistochemical (***C*** – ***E***) and *in situ* hybridization studies (***F***), all x400 with hematoxylin counter-staining and diaminobenzidine chromogen. The lymphoid cells expressed the B-cell marker CD20 (***C***). Lymphoid cells did not express programmed death ligand 1 (***D***). Small numbers of $CD8^+$ T cells were scattered through the tumor (***E***; $CD8^+$). EBER in situ hybridization showed no signals in lymphoid cells (***F***). Scale bar, 20 µm.

PET-CT studies in August 2017. There was no abnormal accumulation of fluorodeoxyglucose (Figure 1B). Her condition has been regularly evaluated since then (overall >42 mo at the time of writing), including PET-CT imaging (June 2018), which found no lesions (Figure 1C). She refused subsequent imaging study, stating that she feels well. We consider her to be disease-free.

DISCUSSION

SR of DLBCL is rare, and although several cases have been reported,[14,15] SR of advanced-stage DLBCL is extremely rare.[17] In this patient, DLBCL was diagnosed by microscopy of a biopsy specimen from the vaginal wall. Although the lung biopsy specimen was technically insufficient, PET-CT SUV suggested that the pelvic and pulmonary lesions were deposits of the same malignancy. The patient's disease was thus considered Ann Arbor stage IV advanced-stage DLBCL.

Most reported cases of DLBCL presenting SR describe localized tumors (stage I). In one review of 18 cases of SR after biopsy, most (*n=15*) were extranodal (stage I).[14] In a different review of 17 cases of SR of DLBCL, most (*n=11*)

were extranodal stage I lymphomas.[15] Low-grade lymphomas have an SR occurrence rate of 5-15%, whereas progressive lymphomas have a low SR occurrence rate.[12] In 209 cases of non-Hodgkin lymphoma, SR was observed in 18 of 140 patients with follicular lymphoma (12.8%) and in 2 of 69 patients with DLBCL (2.9%);[12] these values are only approximations. Treatment for progressive lymphomas usually starts immediately after diagnosis and to identify SR in malignancy requires observation without treatment.

Information on the few cases of progressive DLBCL with SR (n=3) is presented in Table 1.[5,18,19] In 2 patients EB virus was positive,[5,18] and in the third, no information on this point was published. The 2 cases of DLBCL associated with EB virus infection were ABC-type DLBCL, as were most other DLBCL that achieved SR in other reviews.[14,15] We found no infection (including EB virus and HIV-1 and -2) in our patient.

As the cause of SR in lymphoma is unknown, many causes are hypothesized. In almost all cases, SR occurs after biopsy, suggesting that trauma triggers it. Bacterial or viral infections, such as EB virus or HIV, have also been proposed to cause SR. Withdrawal of immune-system suppression may be related to SR, as with cyclosporin for organ-transplant patients,[20] methotrexate for rheumatoid-arthritis patients,[21] or fludarabine for Waldenström-macroglobulinemia patients.[22] Lymphoma cells in one patient whose disease exhibited SR did not express PD-L1 and many tumor-infiltrating $CD8^+$ T cells were found in the biopsied lymph node. These T cells were proposed to have induced apoptosis in the lymphoma cells, causing SR.[16] The lymphoma cells in our patient did not express PD-L1, but $CD8^+$ T cells in small numbers were scattered within the tumor. It was also reported that the presence of ssDNA is a marker for cells undergoing apoptosis, and the disappearance of ssDNA may reflect the process of apoptosis causing SR.[23] What effect they had, and whether they contributed to SR, is matter for speculation. Other than the above, bacterial or viral infection was not relevant, and medications that may have caused SR, such as chemotherapy, steroids, or immunosuppressants, were not taken.

Our patient's disease is, to our knowledge, the only reported case of vaginal DLBCL that underwent SR. Of note, although the average duration of SR is reportedly 13 mo,[24] our patient has remained disease-free for >42 mo, which is the longest interval of SR reported for high-stage DLBCL.

In summary, we describe the very rare phenomenon of SR of stage IV GC-group DLBCL, now persisting for >42 mo. Reports like ours may provide clues to mechanisms of SR of DLBCL and other tumors. Clarifying how SR is initiated may provide insights into tumor biology that permit new treatment strategies.

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Written informed consent was obtained from the patient for publication of this case report and accompanying images.

CONFLICT OF INTEREST

No author has any conflict of interest to disclose.

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Table 1. Published cases of spontaneous regression of advanced-stage DLBCL

Case	Year	Age/ Sex	Site	Staging	Additional Findings	Han's Criteria	Time to SR (Days)	F/U (Months)	Relapse	Reference
1	2013	94/F	Cervical, Axillar, Inguianal Lymph Nodes	III	EBV+	ABC	90	10	Died of pneumonia 10 months later	18
2	2013	85/M	Prostate, Bladder, Multiple Lymph Nodes	III-IV	NA	NA	NA	31	-	19
3	2007	89/M	Inguinal, Supraclavicular Lymph Nodes	III-IV	EBV+	ABC	60	20	16 months later	5
4	2020	76/F	Vagina, Lung, Hilar Lymph Node	IV	EBV-,HIV-	GCB	44	42	-	current case

metastatic melanoma after inoculation with tetanus-diphtheria-pertussis vaccine. Curr Oncol. 2013; 20 : e270-e273.
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